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RUSH-PRESBYTERIAN-ST. LUKE'S

MEDICAL BULLETIN

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VOL. 11 NO. 1 JANUARY 1972

Surgery of the Prostate

Radiology of the Temporal Bone

Hyperalimentation of the Premature Infant

Personality Development and The Medea

Chicago: Patients and Providers

Abstracts

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL BULLETI

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RECENT DEVELOPMENTS IN SURGERY OF THE PROSTATE

Malachi J. Flanagan

Ten percent of hospital admissions in the United States and Canada are for urologic conditions, and it has been estimated that 30 percent of all men above the age of 65 will require some type of prostatic surgery during their lifetime. Prostatectomy is the most frequently performed major operative procedure carried out by urologists and currently ranks fifth among all operations performed.

Carcinoma

Prostatic carcinoma has been found to develop in 18 percent of all men over 50 years of age, and, due to a lengthening life expectancy, its incidence is on the increase.[1]

For the well-differentiated tumor that is clearly confined within the prostatic capsule, radical prostatectomy, usually by the perineal route, offers the only established long-term cure for prostatic malignancy.[2] The operative mortality for radical prostatectomy is strikingly low but permanent postoperative urinary incontinence can be expected to occur in 10 percent of cases, and postoperative impotence is certain to occur. A major role for radical prostatectomy in prostatic cancer has been limited, however, since in the majority of cases, dissemination of cancer outside the capsule to the seminal vesicals, pelvic tissues, lower ureters, pelvic lymph nodes and bones has occurred. More aggressive surgery, including pelvic lymph node dissection, is currently being evaluated as to its effectiveness in improving survival. Lymph node metastases from small primary cancers which had apparently been confined to the prostate area are being demonstrated in these studies.

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Transurethral resection of prostatic cancer with obstruction at bladder outlet and prostatic urethra often provides symptomatic relief when urinary retention has occurred.

The use of estrogens continues to offer symptomatic relief in patients with disseminated disease but its long-term usefulness has been challenged by a recent prospective study which noted a high incidence of cardiovascular and thromboembolic disease in patients receiving estrogens.[3]

Radiation therapy offers potential long-term control of less well-differentiated malignancies of the prostate with extensive local spread and offers the advantage of, theoretically at least, maintaining potency.[4] Radiation therapy for local symptomatic metastatic bone deposits may be associated with dramatic, but usually short-lived, improvement.

Cryosurgery

The application of ultra-low temperatures to hyperplastic and neoplastic tissues of the prostate results in their regular destruction proportional to the time of application of the cryoprobe. Effective freezing of the prostate can be carried out rapidly with minimal blood loss and may require no anesthesia. These features make cryosurgery particularly desirable in the elderly, poor-risk patient with urinary retention.

Cryoprostatic surgery is carried out by insertion of a urethral probe into the re-

gion of the prostate and momentary application of cold, employing a rectal thermocouple as a monitor. The technique is, therefore, a "blind" one since the operator can only estimate by feèl the amount of prostate which requires freezing. Numerous technical problems have been encountered including formation of an "ice ball" of prostatic tissue which requires resection by standard endoscopic methods and delay in the dissolution of sloughed prostatic tissue requiring catheterization for a number of days or even weeks. These factors have thus limited the widespread use of prostatic cryosurgery.

The remission of pulmonary metastatic lesions by application of the cryoprobe to the primary tumor within the prostate has been observed.[5] It has been postulated that the development of *in situ* antibodies by freezing may explain this remarkable phenomenon.

Hemorrhage

Operative and postoperative hemorrhage continue to be a major unsolved problem with prostatic surgery, particularly of the open type. In open prostatectomy, whether by the suprapubic, retropubic, or perineal route, the anatomic position of the prostatic adenoma and residual prostatic fossa within the deep pelvis often restricts complete and accurate placement of hemostatic sutures and application of cautery. The raw prostatic fossa, after enucleation, very often continues to bleed for a number of days postoperatively, and although the degree of hemorrhage is not alarming, it is associated with painful and debilitating bladder spasms. Prostatic tissue is rich in the enzyme fibrinolysin which may be liberated in large amounts with prostatectomy to further complicate the problem of hemorrhage.

In an effort to reduce the severity of arterial hemorrhage during prostatectomy from most of the numerous arterial branches supplying the prostate, bilateral internal iliac artery legation has been carried out with prostatectomy.[6] A preliminary evaluation of this technique has shown a slight reduction on the amount of hemorrhage incurred at the time of surgery but no significant decrease in the degree of hemorrhage postoperatively.

Choice of Operation

Indications for the numerous and various operative approaches to the prostatic have become standardized (Figure 1). The open method of prostatectomy, whether by suprapubic, rétropubic, or perineal route, is advantageous when larger degrees of prostatic hypertrophy are encountered and tends to be associated with less requirement for reoperation in later years. It is ideally suited for the younger patient who has a large prostate weighing over 50 grams. The major disadvantage to open prostatic surgery is its higher mortality rate, a greater degree of bleeding, both operatively and postoperatively, and increased postoperative morbidity, and a longer period of time required for hospitalization. The open method of prostatectomy tends to be less precise and definitive with smaller prostates associated with fibrous inflammatory reaction.

Endoscopic removal of adenomatous hypertrophied portion of the prostate is used three times as often as all other methods of prostatectomy combined. The preeminent position of transurethral prostatic resection commonly referred to as the TUR, is supported by its very low mortality rate and favorable functional results obtained in the operative management of mild-to-moderate hypertrophies of the prostate producing obstruction.

Transperineal Urethral Resection

A major complication of the TUR is development of postoperative anterior urethral strictures. In an effort to reduce or eliminate the occurrence of stricture, routine employment of perineal urethrostomy with TUR has been carried out and is referred to as transperineal urethral resection (TPUR). See Figure 2.

The problem of stricture has been recognized for many years (Figure 3). Its occurrence is reported to follow 16 to 20 percent of all TURs, and its development

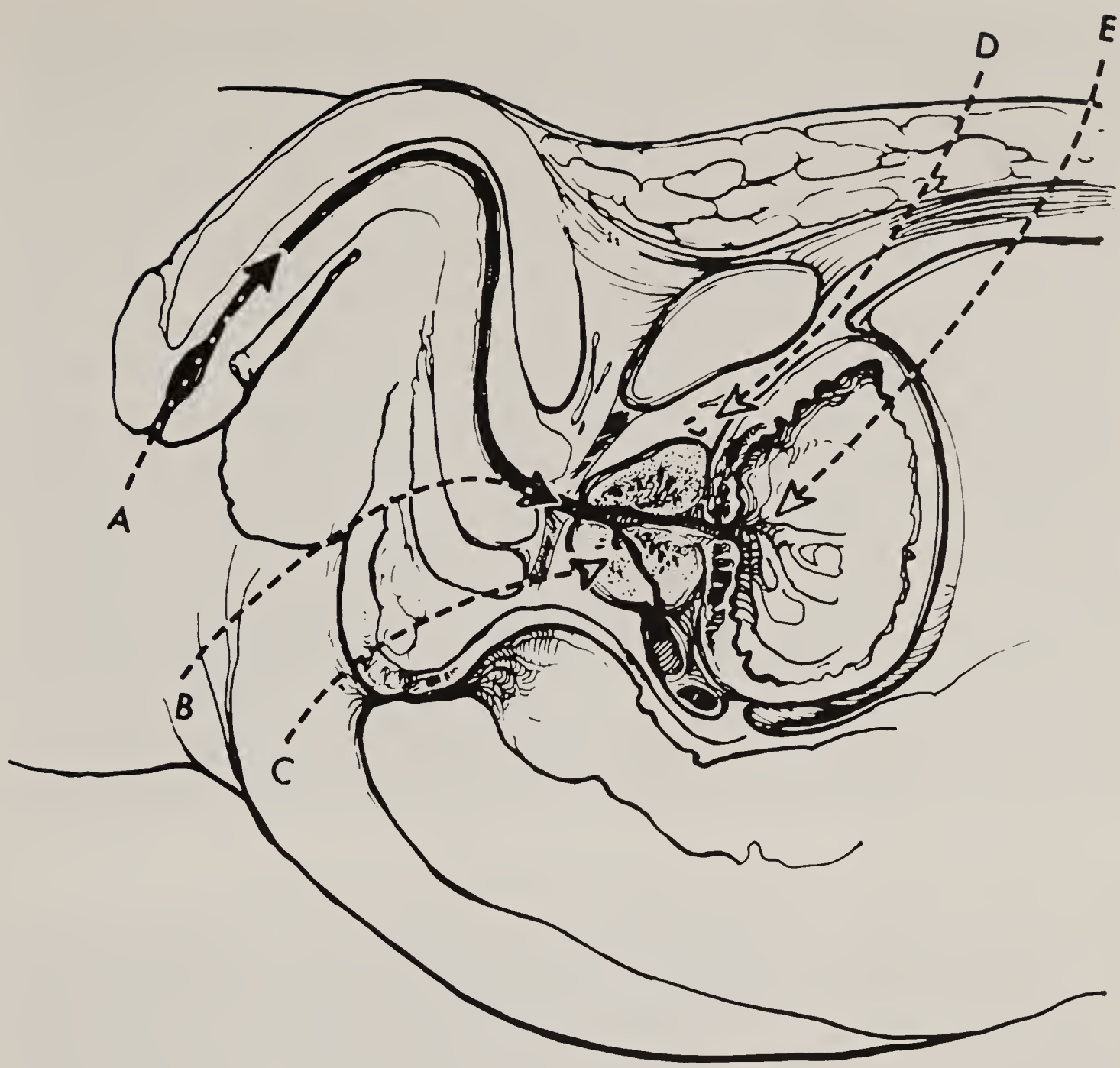

Fig. 1—Operative approaches to the prostate. (A) transurethral; (B) transperineal urethral; (C) perineal; (D) retropubic; (E) suprapubic. (*From*: Intensive Care of the Surgical Patient, Marshall D. Goldin, Ed. Reproduced, with permission of Year Book Medical Publishers, Inc., Chicago, p. 459.

may completely nullify the effects of prostatic surgery. Anterior urethral strictures occur most frequently in the terminal urethra, but may develop in any location along the anterior urethral canal. The degree of stricture formation may be mild, requiring an occasional urethral dilation or two, but it can be severe, disabling and painful, necessitating filliform dilatations over an extended or indefinite period of time.

Strictures occur for a number of reasons. The large-caliber resectoscope required for resection fits rather snugly into the relatively rigid, terminal male urethra and quite tightly in the anatomically small, or strictured, urethra. This latter condition has been shown to exist in 24 percent of all men undergoing transurethral resection. Urethral trauma and injury may be produced by the in-and-out movement of the resectoscope very often required for the performance of resection. When more pronounced degrees of prostatic hypertrophy are removed by the endoscopic route, more operative time is usually required, and it is reported that the occurrence of postoperative stricture approaches 30 percent in such instances.[8] Postoperatively, a

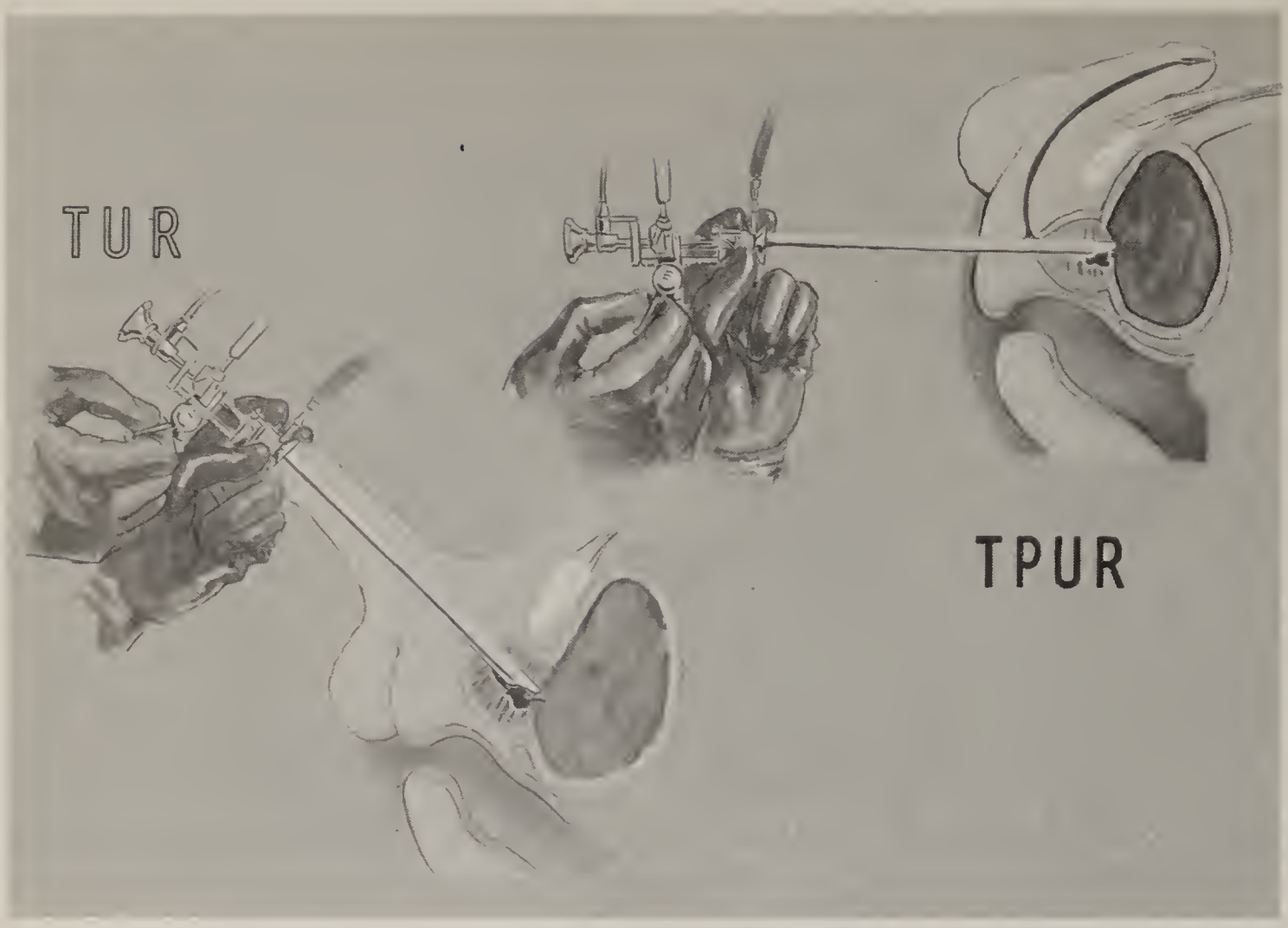

Fig. 2—TPUR affords greater instrument mobility during excision of prostatic tissue.

large-caliber, indwelling catheter is present for a number of days in the already traumatized urethra. If catheter traction for purposes of hemostasis is required, further urethral trauma may be produced at various pressure points along the urethra. By the routine employment of catheter drainage through the perineum with transperineal urethral resection, this problem is largely eliminated (Figure 4).

The employment of a separate perineal opening for introduction of the resectoscope is not a new idea. The perineal urethra is the largest and most elastic portion of the urethra and thus accepts more readily the large 24 to 28 French instruments required for resection. Proponents of this technique have employed it when any preoperative urethral snugness is detected or when any hinderance to free maneuverability of the resectoscope is experienced. The few extra minutes, so it is said, required for carrying out perineal urethrostomy might save the patient two years of postoperative dilatations. In spite of these considerations perineal urethrostomy was seldom carried out, even when demonstrable tightness of the urethra to the instrument was apparent. As routinely practiced, the procedure often had been time consuming and tedious, direct exposure of the urethra and suture of the urethra edges was necessary, and a surgical assistant was often required because the urethra would retract into the depths of the perineum.

The operative method developed for TPUR requires only a scalpel, a Mandarin stylet, and an extra #24 F resectoscope sheath and obturator, in addition to the standard resection instruments. Surgical assistants are not necessary. After calibration of the urethra with a #25 or #26F Sound, perineal urethral insertion of the resectoscope is carried out (see Figures 5*a* to 6*f*). Endoscopic resection of the prostate is thereafter carried out (see Fig. 7*g*). With all anterior urethral resistance to resectoscope movement

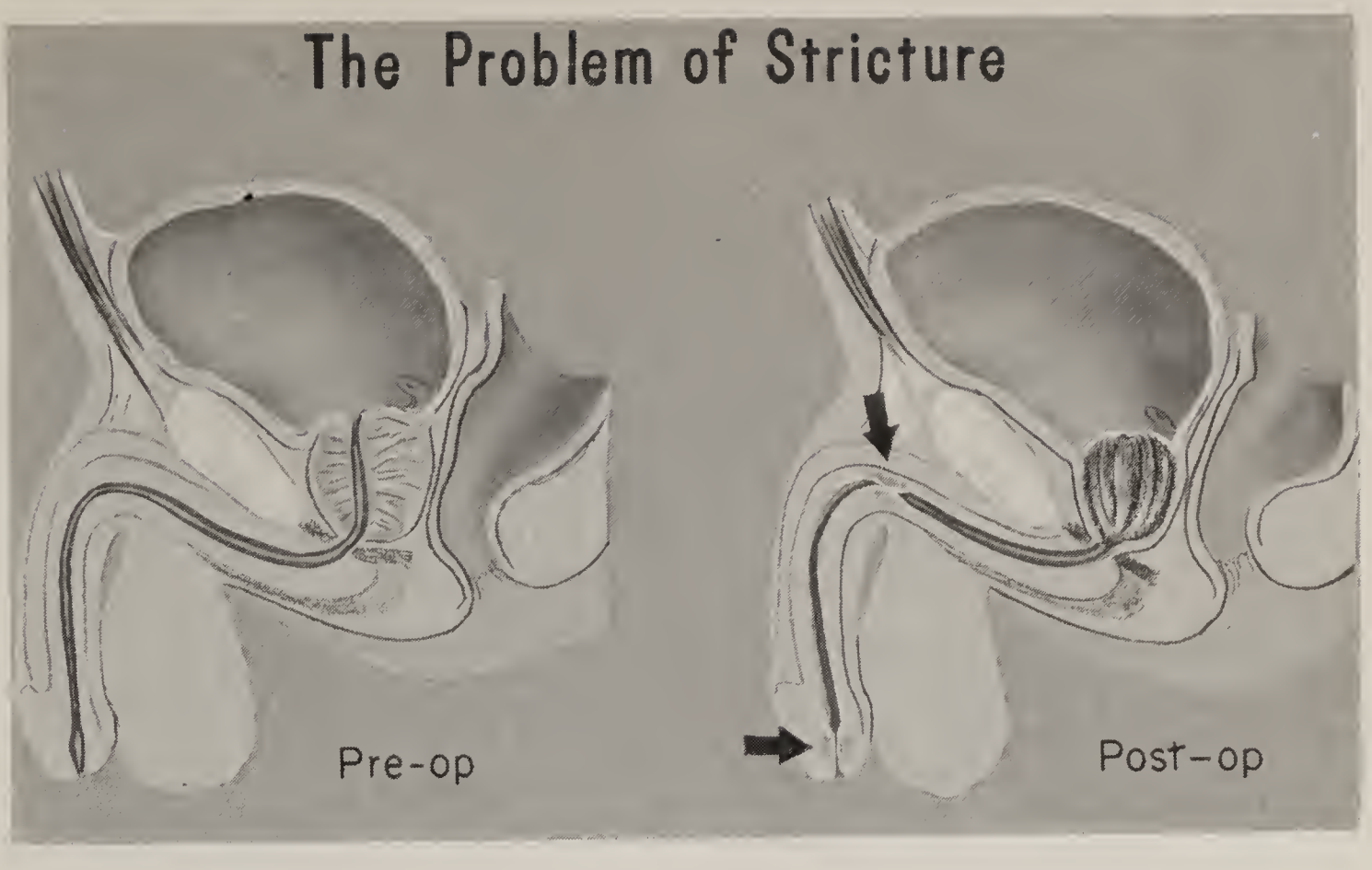

Fig. 3—Postoperative stricture formation following TUR may occur anywhere along the anterior urethral canal.

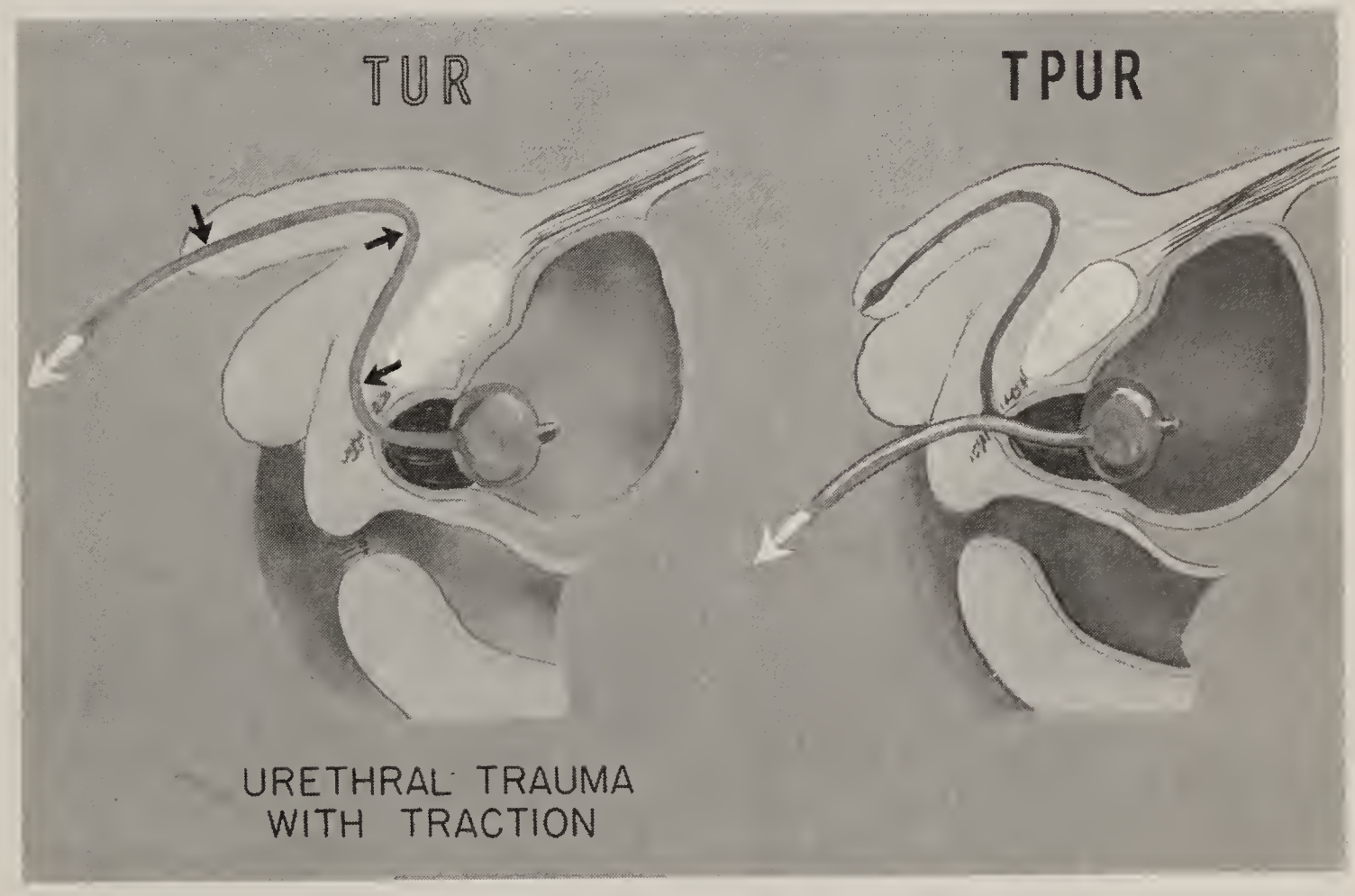

Fig. 4—With TPUR, the perineal urethrostomy opening is employed for catheter drainage postoperatively.

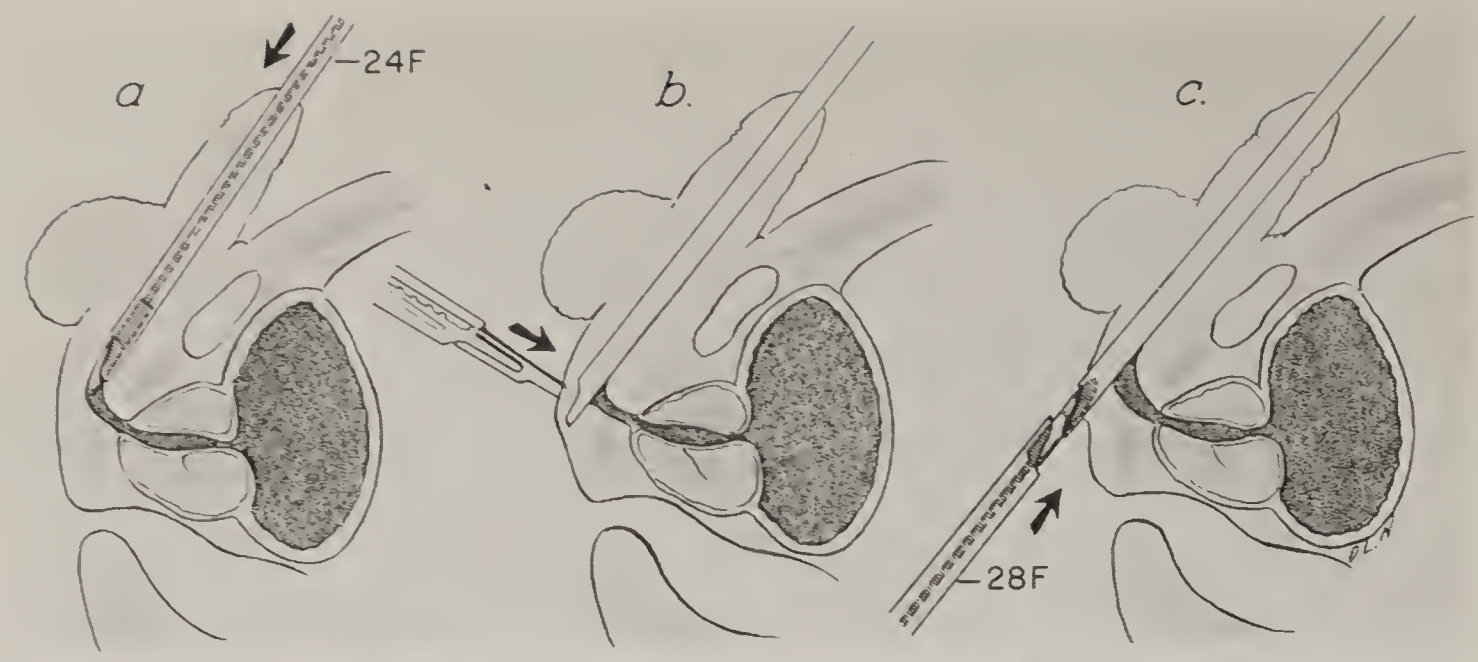

Fig. 5—Transperineal Urethral Resection of the Prostate. (a) #24#F sheath and obturator are placed in perineal urethra (b) The obturator has been removed, incision made in the grooved portion of the #24#F sheath, and the sheath end "popped" out of the perineum. (c) The #28#F sheath and obturator are "locked" into the #24 sheath.

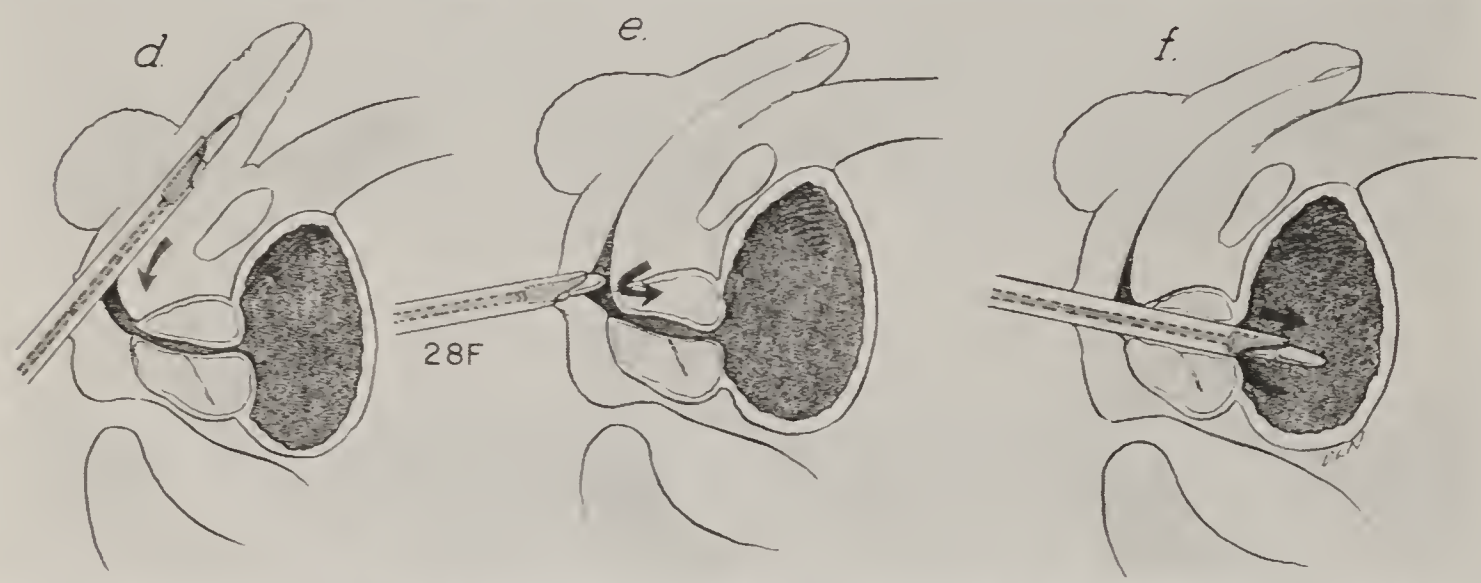

Fig. 6—Transperineal Urethral Resection of the Prostate, *cont.* (d) The #28#F sheath and obturator has been delivered into the pendulous urethra. (e) and (f) The sheath and obturator's direction is reversed and the instrument passed into the bladder.

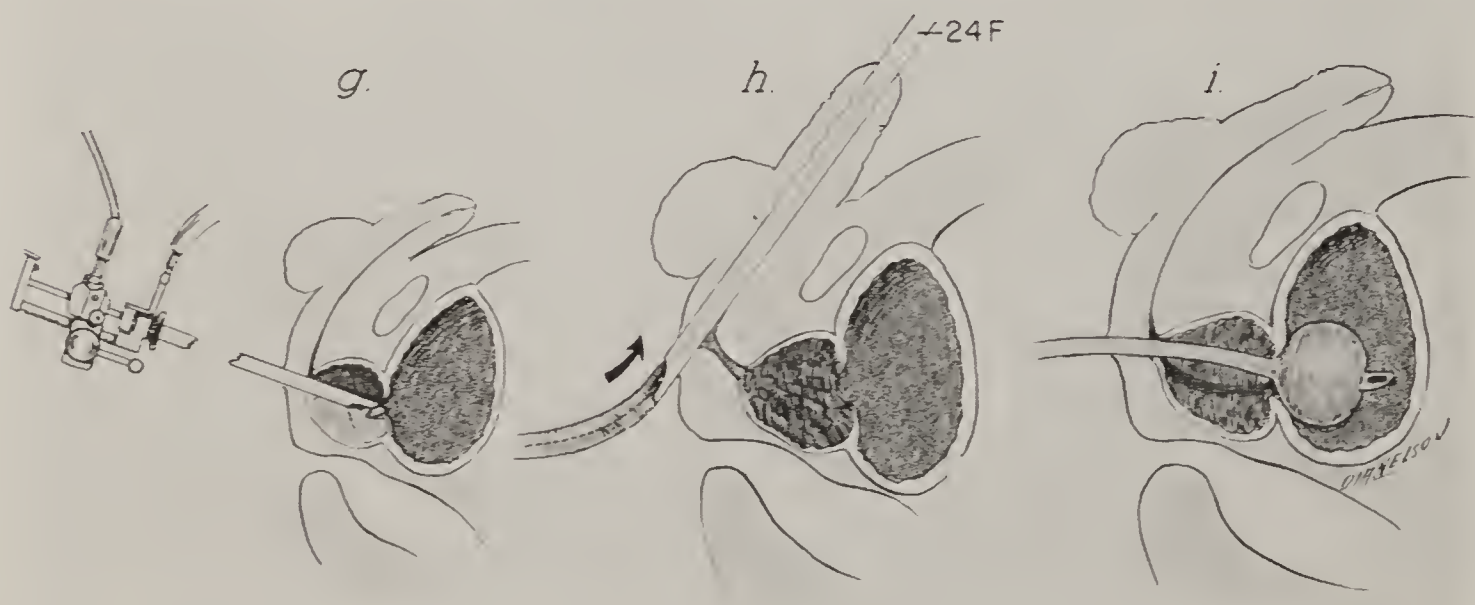

Fig. 7—Transperineal Urethral Resection of the Prostate, *cont.* (g) Endoscopic resection of the prostate is carried out. (h and i) Technique of insertion of catheter. The perineal urethrostomy opening is re-identified by reinsertion of the #24 sheath and obturator, and a catheter supported by a stylet is thereafter delivered into the pendulous urethra, reversed, and passed into the bladder.

eliminated, greater mobility of the instrument is experienced, and in many instances, an overall reduction in operative time is accomplished. Upon completion of the resection, a large-caliber Foley catheter is directed into the bladder (Figures 7*h*, *i*) and left dwelling in the perineal urethra for three to five days. A perineal catheter is usually more comfortable than a urethral catheter. Free drainage of secretions occurs, and crusting is seldom seen around the edges of the emergency catheter.

By routine use of TPUR, the incidence of postoperative urethral stricture has been reduced to 2.79 percent. If catheterization along the entire urethral length was avoided, both pre- and postoperatively, the incidence of stricture was reduced even further, to 1.12 percent. No permanent urethroperineal fistulas occurred. Seventy percent of patients were voiding by normal routine in two days and 94 percent within four days. Fistula closure often could be aided by instructing the patient to exert digital pressure on the perineal opening when voiding.

Familiarity with transperineal urethral resection is accomplished easily, and, once achieved, becomes a routine urologic maneuver. In addition to being virtually free of complications, TPUR affords greater ease of resection over TUR. TPUR has significantly reduced the incidence of postoperative anterior urethral strictures, and thus appears to be an acceptable and highly desirable alternative to TUR when endoscopic surgery of the prostate is carried out.

Summary

Current surgical therapy for benign and malignant diseases of the prostate is discussed. The common problems of prostatic surgery, hemmorhage, and stricture are reviewed. The advantages of the technique of transperineal urethral resection are described and their importance emphasized.

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RADIOLOGY OF THE TEMPORAL BONE: RECENT APPLICATIONS OF LAMINOGRAPHY

Jerry P. Petasnick
Michael S. Huckman

Radiologic examination of the temporal bone is essential in the evaluation of abnormalities associated with changes in its osseous structures. Until recent years, these examinations have been of limited value because of the confusing superimposition of structures located in different planes. Multiple radiographic projections have been devised in an attempt to overcome this problem; however, the resultant distortion produced by the angulation of the patient's head and the x-ray beam makes it difficult to correlate radiographic and surgical findings. The major drawback to the conventional radiographic examination of the ear, however, is its inability to define the small structures of the ear. The development and application of microsurgical techniques has presented the radiologist with the challenge to provide a corresponding improvement in the radiography of the middle and inner ear.

The application of laminography to the investigation of the ear provided a major impetus to the improvement in radiographic technique. Laminography (tomography, planigraphy, stratigraphy, body section radiography) is a technique which allows visualization of a desired structure while obscuring or blurring those structures in front of or behind it. Unidirectional or linear laminographic techniques such as used to study lung masses were used initially to examine the ear; however, these were unsatisfactory because of inadequate blurring of structures outside the plane of interest. As a result, disturbing shadows were superimposed upon the structures of prime interest. In addition, the thickness of the sections obtained was too great to allow separation of the small structures of the ear. In recent years several laminographic units have been developed, one of which is currently being used in our Department of Diagnostic Radiology (Figure 1) which overcome the major objections of linear tomography. Objects as close as 1.0 mm can be readily separ-

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ated so that the small structures such as the incus or malleus can be identified.[1]

When applied to areas such as the ear, the laminographic examination must be sufficiently refined so that it is possible clearly to separate structures in close approximation. For example, it is desirable to identify structures such as the ossicles, oval or round window, or semicircular canals; with the present multidirectional laminographic units these anatomic parts can be easily examined. The resultant increase in anatomic details has made laminography an integral part in the diagnosis and management of otologic disease. This is particularly true

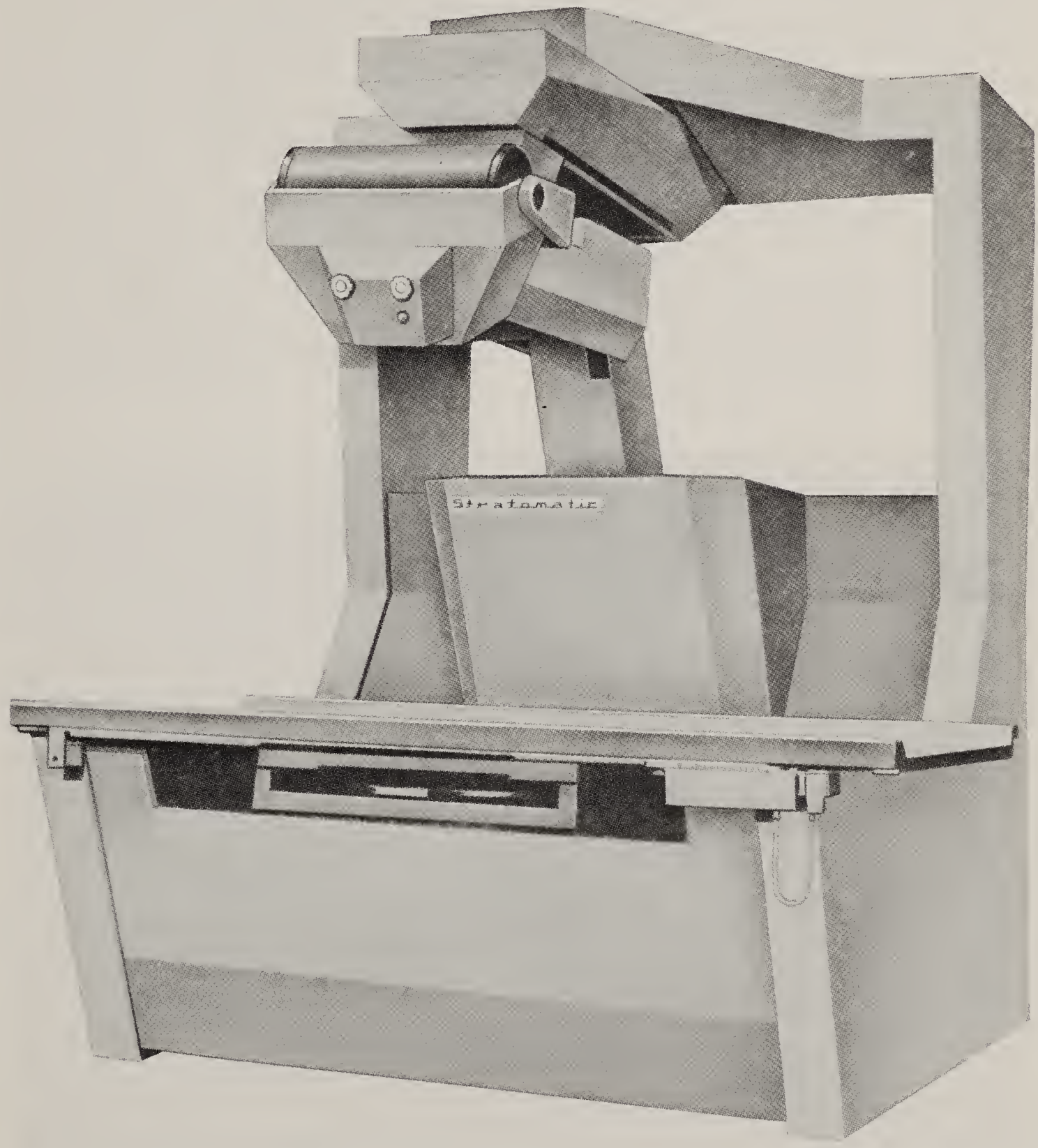

Fig. 1—Multidirectional laminographic machine currently in use at PSLH.

with regard to the middle ear. Since its structures cannot easily be visualized by direct examination, it is the most difficult area to evaluate clinically, and it is the area most commonly involved by pathologic processes. Laminography of the ear has become the roentgenographic examination of choice because of the increased information provided.[2]

Although several reports were published in the late 1950's regarding laminography of the ear, the major impetus to the development and refinement of these techniques has been the work of Valvassori.[3] Laminographic examination of the temporal bone consists of multiple sections obtained 1 or 2 mm apart. Through the use of appropriate projections, usually frontal and lateral, a three-dimensional image of the temporal bone can be constructed, and osseous abnormalities of the external, middle and inner ear readily recognized.

Figure 2 is a frontal section obtained through the anterior portion of the right external auditory canal. The structures seen on film lie in a plane perpendicular to the saggital plane of the skull. The external auditory canal, epitympanic recess (attic) and tympanic cavity are visualized. The lateral wall of the epitympanic recess and superior wall of the external auditory canal join to form the scutum, or radiologic spur, which is the superior point of attachment of the tympanic membrane. Just medial to this, the head of the malleus can be identified as a club-shaped structure in the epitympanic recess. The handle of the malleus extends downward towards the tympanic membrane. This is the portion of the malleus which can be identified on external examination of the ear. Medial to the tympanic cavity is the otic capsule. In this particular section the apical and middle turns of the cochlea can be identified. The apex or medial aspect of the petrous pyramid is well seen in this projection.

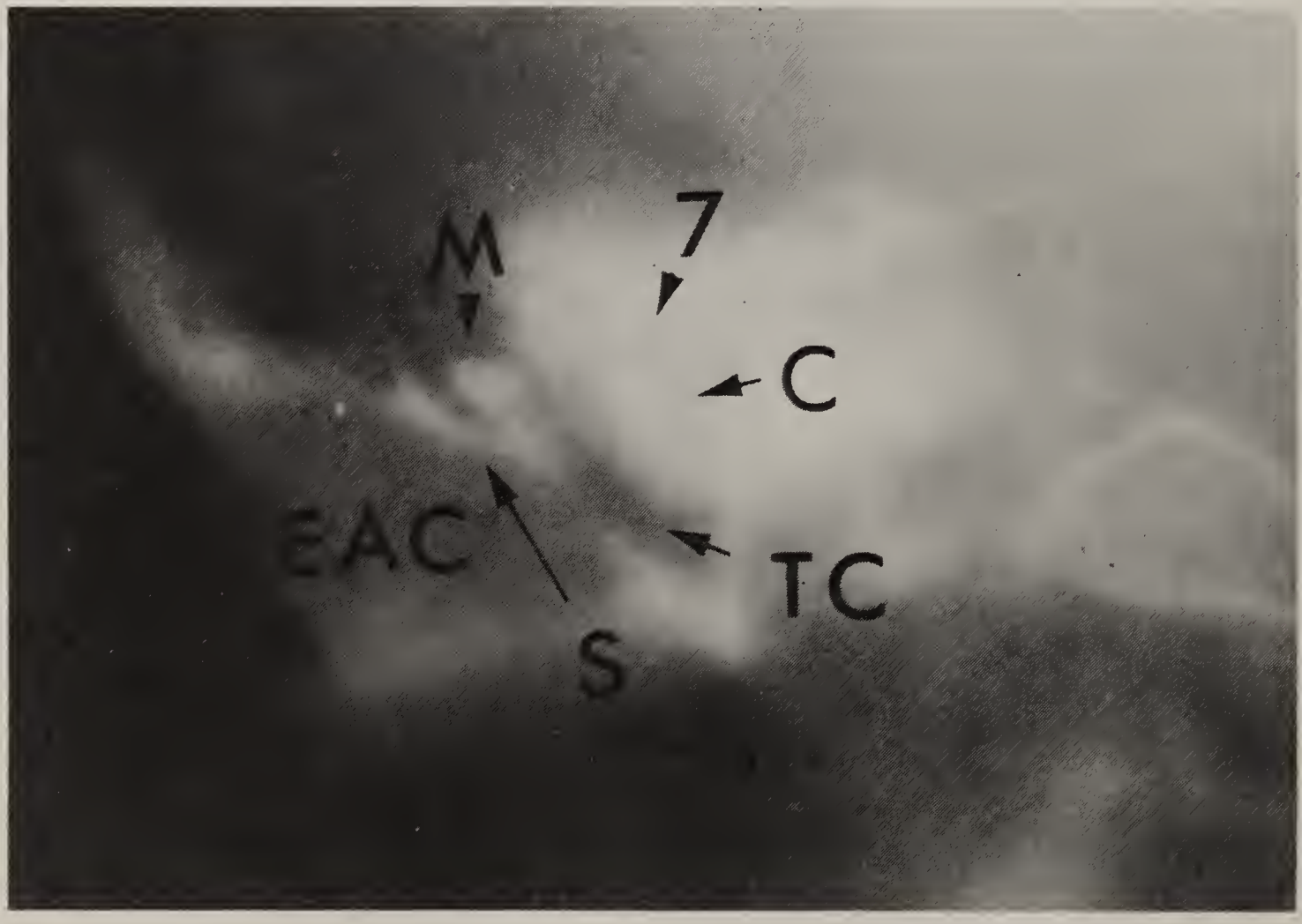

Fig. 2—Normal frontal tomogram through the anterior portion of the external auditory canal. EAC-external auditory canal; TC-tympanic cavity; S-spur; M-malleus; C-cochlea; 7-7th nerve canal.

Figure 3 is a frontal section through the mid-portion of the external auditory canal and petrous pyramid. The external auditory canal, tympanic cavity and epitympanic recess are again identified. The ossicular structure in this section is the long process of the incus which is positioned in the epitympanic recess. Note that in comparing this section with the previous section (Figure 2) the malleus and incus are clearly separated. The osseous structures of the otic capsule which enclose the membranous labyrinth are readily identified. The vestibule and basilar turn of the cochlea (promontory) can be seen. Arising from the vestibule are the semi-circular canals. On the lateral aspect of the vestibule there is a dehiscence between the horizontal semi-circular canal superiorly and the promontory of the cochlea inferiorly. This is the vestibular or oval window. This apparent opening occurs because the normal footplate of the stapes which occupies the oval window is of insufficient thickness to produce any linear density. This area is of considerable importance in evaluation of patients with otosclerosis, since patients with this disease will usually have an abnormality of the footplate of the stapes which can be detected radiographically.

Figure 4 is a frontal section 2 mm posterior to the previous section (Figure 3). This more clearly delineates the vestibule, anterior lumen of the horizontal semi-circular canal and the basilar turn of the cochlea. Medial to the vestibule is the internal auditory canal. A fine bony spicule called the *crista falciformis* can be identified, which divides the internal auditory canal into superior and inferior compartments. The anterior contains the 7th nerve and nervus intermedius anteriorly and the superior vestibular division of the acoustic nerve posteriorly. The larger inferior compartment contains the cochlear nerve anteriorly and the inferior vestibular nerve posteriorly. This structure is of importance in the

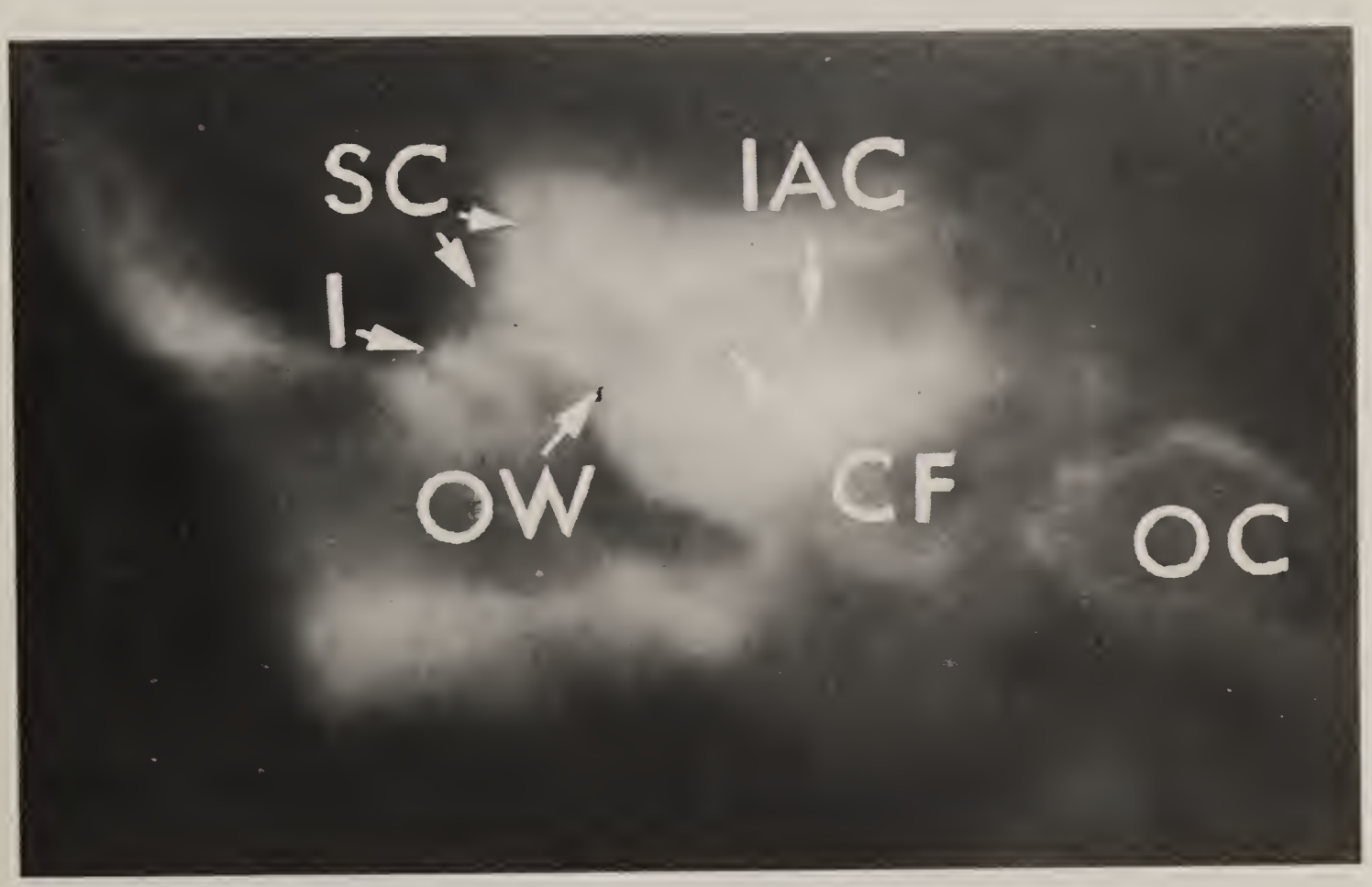

Fig. 3—Normal frontal tomogram 4 mm. posterior to Figure 2. I-incus; SC-semicircular canals; OW-oval window; IAC-internal auditory canal; CF-crista falciformis; OC-occipital condyle.

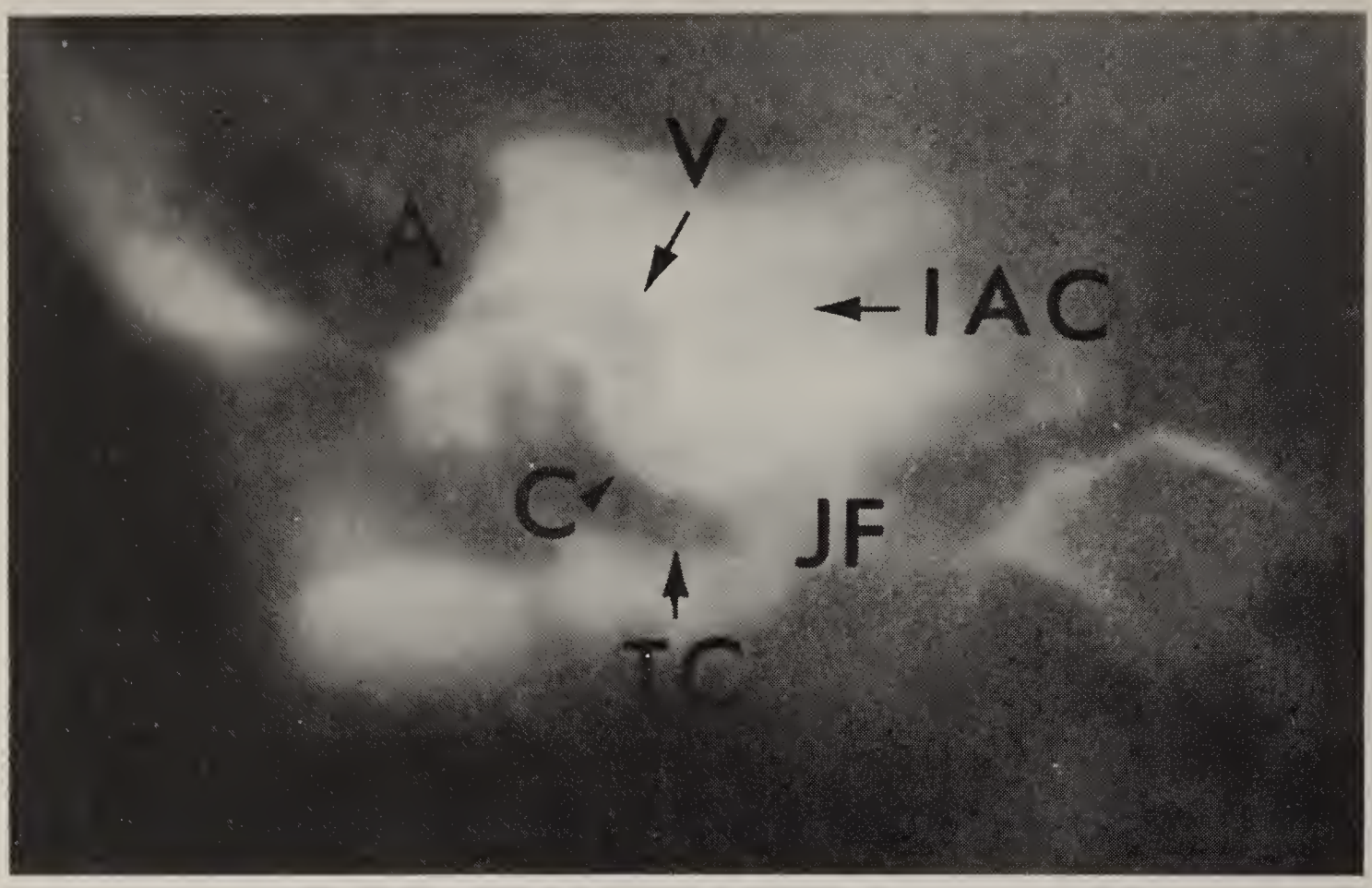

Fig. 4—Normal frontal tomogram 2 mm. posterior to Figure 3. A-mastoid antrum; V-vestibule; C-cochlea; JF-jugular foramen.

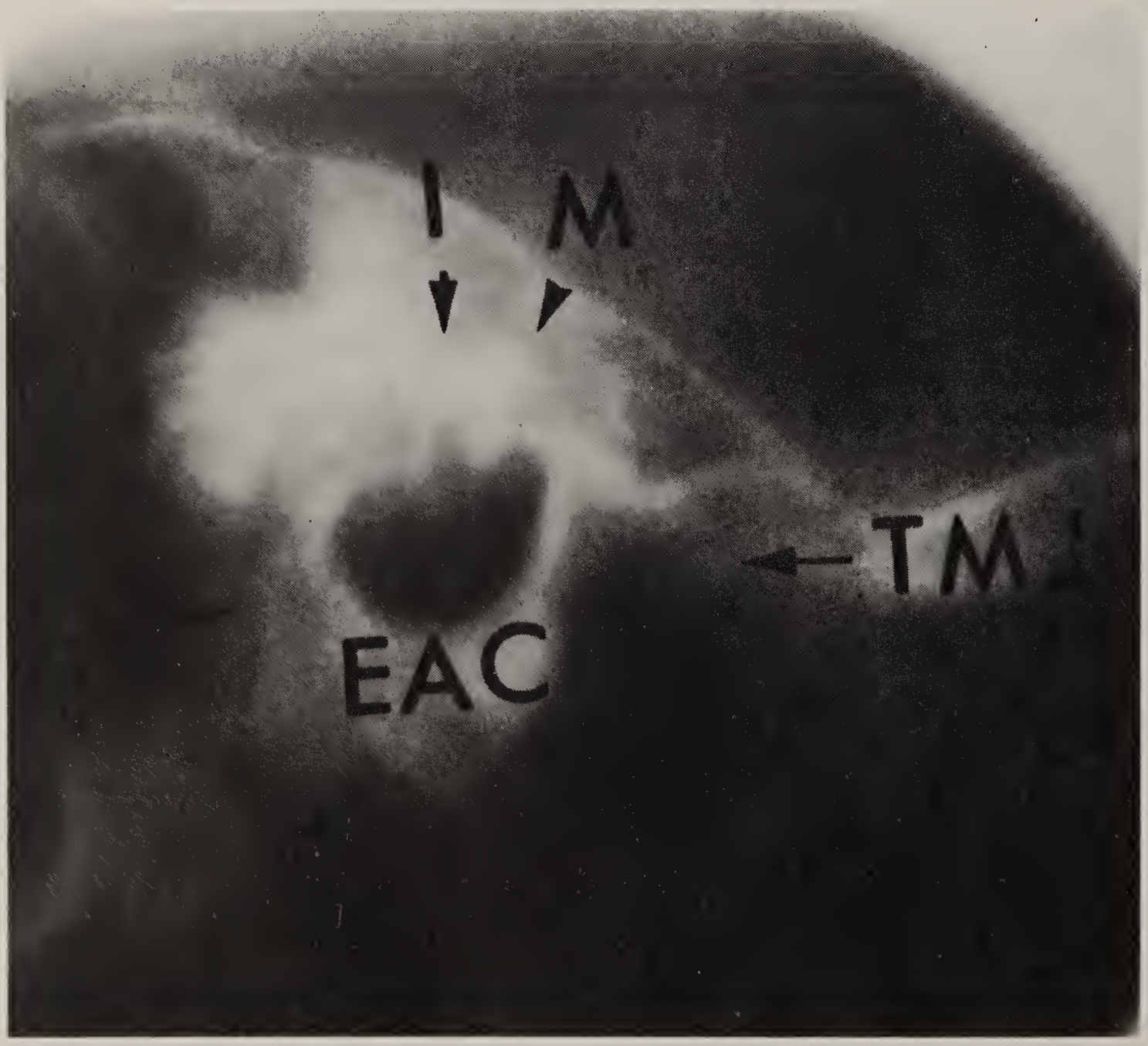

Fig. 5—Normal lateral tomogram at the level of the ossicles. The malleus (M) is anterior and the incus (I) posterior in the epitympanic recess. The roof of the epitympanic recess, the tegmen tympani; is best evaluated in this projection. The vertical portion of the 7th nerve canal lies just behind the external auditory canal.

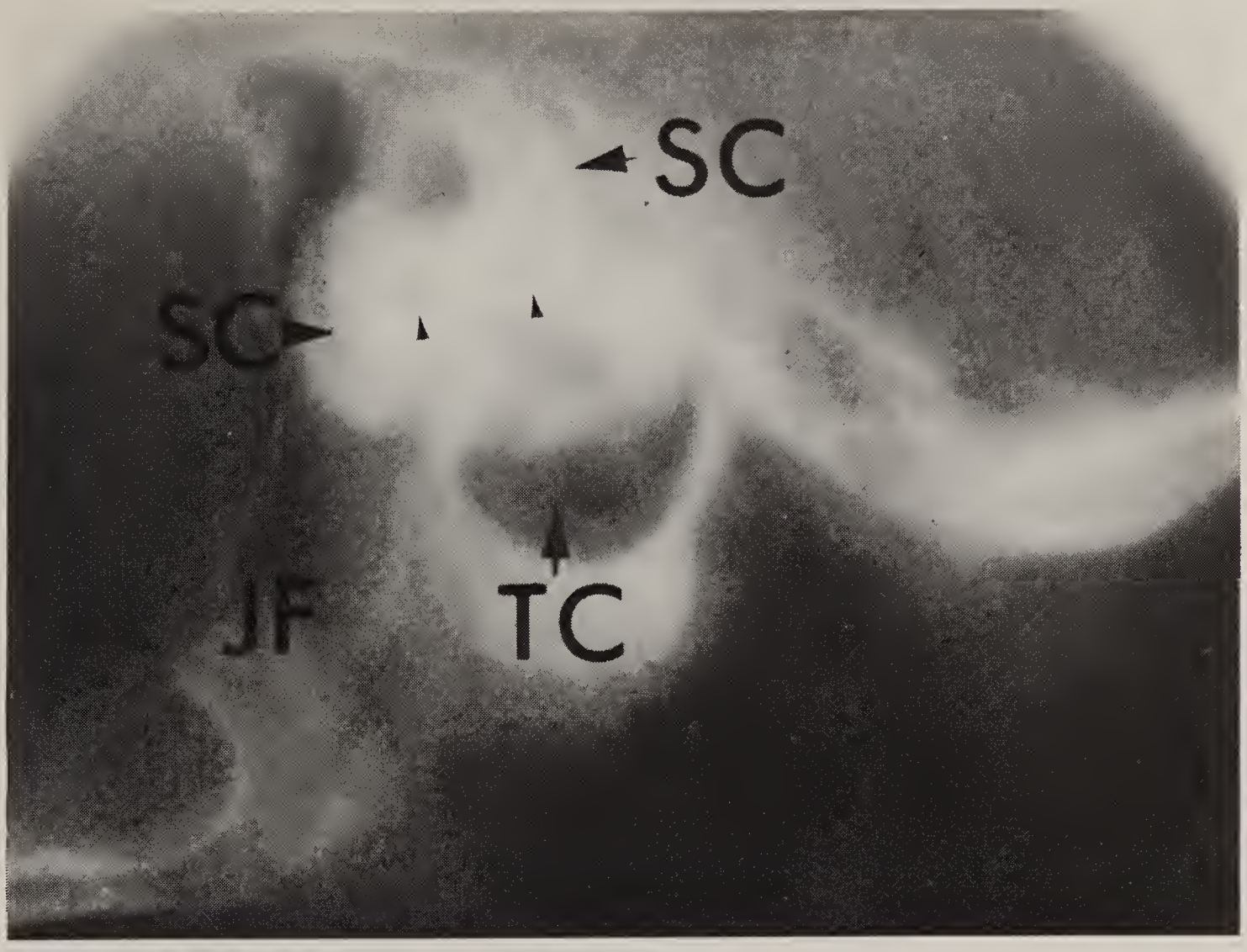

Fig. 6—Normal lateral tomogram 2 mm. medial to Figure 5 demonstrating the tympanic cavity (TC), superior and posterior semicircular canals (SC), and the jugular foramen (JF). The two holes above the tympanic cavity are the anterior and posterior limbs of the horizontal semicircular canal (arrows). The posterior fossa is on the left, the middle fossa on the right.

early diagnosis of acoustic neurinomas, which usually arise from the inferior vestibular nerve.

Figure 5 is a lateral section at the level of the ossicles. The ossicular mass in this projection consists of the head and handle of the malleus anteriorly and the body and long process of the incus posteriorly. The tegmen tympani, which forms the roof of the epitympanic recess, is best seen in this projection. Evaluation of this area is important in determining the thickness of bone separating the middle ear cavity and dura. The medial portion of the external auditory canal can be identified. Just posterior to the external auditory canal is the vertical portion of the 7th nerve canal extending to the stylo-mastoid foramen. The temporo-mandibular fossa and mandibular condyle can also be seen anterior to the external auditory canal.

Figure 6 is a lateral section 2 mm medial to the section in Figure 5. This section extends through the mid-portion of the tympanic cavity, which has a crescent shape open superiorly about the promontory of the cochlea. Portions of the semi-circular canals are well visualized.

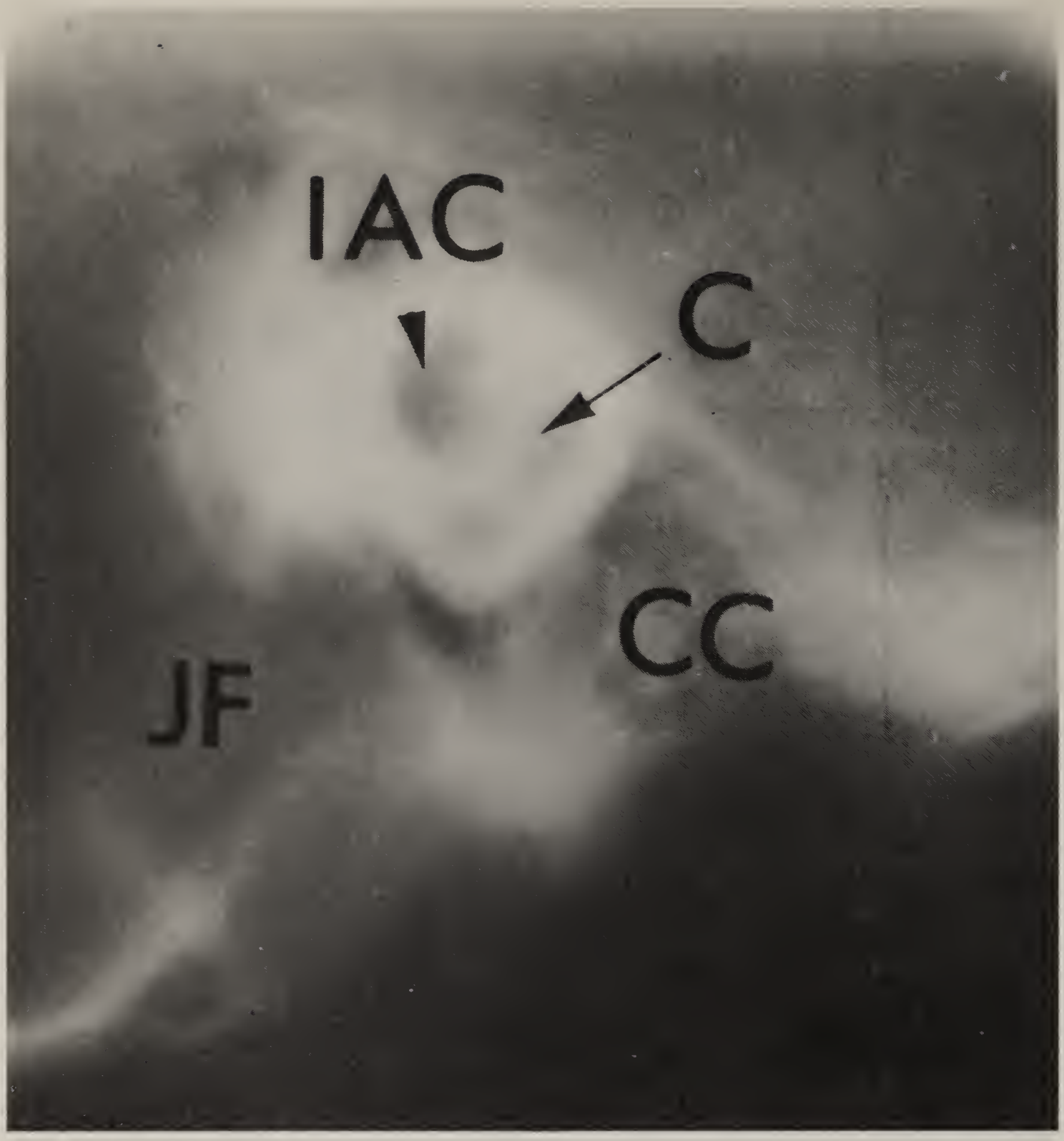

Fig. 7—Normal lateral tomogram 6 mm. medial to Figure 6 demonstrates the internal auditory canal (IAC) and cochlea (C) and their relation to the jugular foramen (JF) and carotid canal (CC).

Figure 7 is a lateral section 6 mm further medial and is through the lateral aspect of the internal auditory canal. Anterior to the internal auditory canal is the cochlea. The carotid canal lies anterior and inferior to the internal auditory canal; the jugular foramen is posterior and inferior.

Figure 8 is a basilar view of the petrous pyramids and foramen magnum. Structures which can be identified include the external auditory canal, petrous apex, jugular foramen, hypoglossal canal containing the 12th nerve, and foramen magnum. In addition, the foramen ovale, which contains the mandibular branch of the 5th nerve, and foramen spinosum, which contains the middle meningial artery, can also be seen in the floor of the middle fossa.

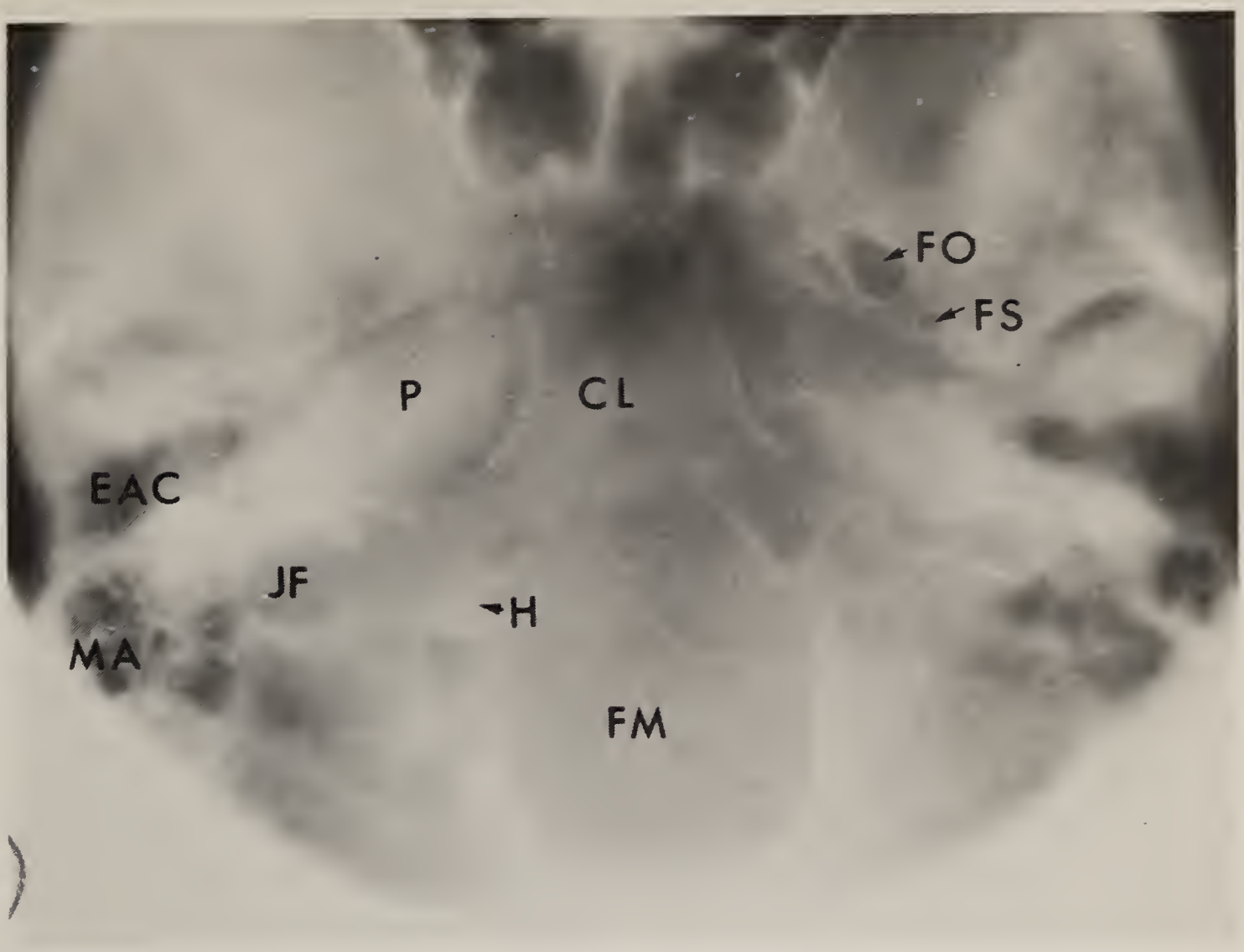

Fig. 8—Normal horizontal tomogram at the level of the jugular foramen (JF) and hypoglossal canal (H). FM-foramen magnum; CL-clivus; FO-foramen ovale; FS-foramen spinosum.

The above illustrations demonstrate the type of information which can be achieved by the current techniques of laminography. Laminography has been extensively used in studying congenital abnormalities, middle ear infections, trauma, otosclerosis, and temporal bone tumors.[4] Because of the resultant anatomic detail, pluridirectional laminography has become indispensable in roentgenographic examination of the ear.

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TREATMENT OF THE PREMATURE INFANT BY HYPERALIMENTATION: A PRELIMINARY REPORT

Charles D. Goodwin
Howard Levy
Richard G. Caldwell
Joseph R. Christian
Frank R. Johnson

In spite of many advances in the treatment of infants, mortality in the premature infant remains quite high. The management and feeding of premature infants is difficult, and weeks and even months are required in order to achieve an adequate weight prior to discharge from the hospital. Premature infants frequently suck poorly, and oral feedings, as well as feedings by gavage, are all too frequently associated with aspiration. The hazards of aspiration are very real in the premature infant. This is particularly true in those who have had perinatal asphyxia or respiratory distress because they are often hypotonic and have decreased gastrointestinal motility.[1] Such infants are poor candidates for early oral feeding, although their need for fluid and calories is more urgent.[2,3] It is important for the premature infant quickly to resume the rate of weight gain similar to that which occurred *in utero*. This is true both for premature infants and those who are small for gestational age.[4] The rapidity with which an infant resumes his intrauterine growth rate may determine his ultimate prognosis.[4] Thus, it is imperative that increased calories and protein be supplied to these infants from the very beginning of life.

Very small babies are poorly equipped to spare body protein in the face of prolonged starvation.[5] Glycogen stores are very small, and fat is virtually absent in babies under 1500 gm. Aherne and Hull have demonstrated total depletion of the brown adipose tissue within three or four days of birth in babies who were small for

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date.[5] This situation is rarely encountered under other conditions.

McCance and Widdowson have demonstrated in rats that undernutrition for a short period early in life resulted in permanent retardation of growth even if the animals were later fed maximally.[6]

Nutrition inadequate in calories and protein, coinciding with the period in life in which the brain is growing most rapidly, produces a brain which is smaller at maturity than in control animals and which also matures biochemically and functionally at a slower rate.[7,8] Winick and Noble have also demonstrated that in rats neither the deficit in brain size nor the DNA concentration resulting from a restricted diet in the early days of postnatal life could be repaired by subsequent feeding.[8] Fish and Winick have shown that the cerebellum is retarded early whereas the duration of malnutrition must be longer before cerebral cell division is slowed down.[6] These animal experiments correlate with findings demonstrated in human infants who have received inadequate calories and protein during the early period of life. Winick has found a reduced number of cells in the brains of infants who died of malnutrition during the first year of life.[9] Stoch and Smythe have suggested that undernutrition during infancy may inhibit the growth of the brain.[5] Drillien has found a high incidence of brain damage in prematurely born children who were treated with initial starvation.[10] Churchill has found that babies with cerebral palsy had taken longer to regain their birthweight than had normal babies.[10]

The requirements of the low-birth-weight infant have been studied by a number of investigators. Gordon and Levine have demonstrated that an intake of 120 to 130 calories/kg/day should supply the low-birth-weight infant with sufficient calories for resting metabolic needs, physical activity expenditures, losses incurred during feedings, and for growth requirements.[11] The requirement of protein in the low-birth-weight infant is about 4 gm/kg/day.[11,12]

It is often difficult to supply the premature infant with this quantity of nutrient orally or by gavage, and it is entirely impossible with presently available peripherally administered intravenous infusions. In addition, sucking and swallowing result in fatigue, with increasing nutritional deficits and a higher incidence of aspiration pneumonia. Raffensperger, et al. did a well-controlled study in which they treated low-birth-weight infants with a feeding gastrostomy. They reported an increased morbidity and mortality with this method due primarily to wound infection and sepsis and concluded that the feeding gastrostomy was not a useful adjunct in the treatment of the low-birth-weight infant.[13]

Encouraged by the excellent result obtained in children who were maintained on hyperalimentation with hypertonic parenteral infusions of dextrose and amino acids because of gastrointestinal tract anomalies, the authors elected to try this technique on an infant who was gradually deteriorating with conventional management. In spite of some problems managing the first infant the results exceeded our expectations, and we have subsequently used hyperalimentation to supplement oral feedings in a series of 10 infants with birth weights of less than 1500 gm or those with respiratory distress and birth weights of less than 1750 gm in order to evaluate the role of hyperalimentation in the treatment of the premature infant.

CASE REPORTS

The 10 premature infants treated with hyperalimentation may be divided into two groups. Cases 1 to 7 were infants not requiring a respirator prior to hyperalimentation. Cases 8 to 10 were infants with a respiratory distress requiring a respirator soon after birth. The 10 cases are outlined in Tables I and II. Cases 1,4,5, and 8 are discussed in more detail.

TABLE I

PREMATURE INFANTS WITH NO RESPIRATORY DISTRESS OR WITH RESPIRATORY DISTRESS NOT REQUIRING A RESPIRATOR

Case	Birth Weight (gm)	Estimated Gestational Age	Early Complications	Complications After Beginning Hyperalimentation	Days of Hyper-alimentation	Discharge Weight (gm)
1.	964	28 weeks	Sepsis X3 Frequent apnea Gradual deterioration and weight loss	Hyperglycemia Metabolic Acidosis Calcium carbonate precipitate in catheter	21	2098
2.	1739	32 weeks	Mild R.D.S.	None	13	2325
3.	1183	28 weeks	Moderate R.D.S.	Mild aspiration pneumonia	41	2325
4.	1729	32 weeks	Moderate R.D.S.	None	14	2268
5.	1332	30 weeks	None	Massive aspiration with arrest Wound infection (coagulase positive Staphylococcus and Candida albicans Blood culture positive for coagulase positive Staphylococcus	21	2041
6.	1389	30 weeks	Moderate R.D.S. Hyperbilirubinemia	Transiently elevated B.U.N. Hyperbilirubinemia requiring exchange transfusion Mild aspiration pneumonia X2 Massive aspiration with respiratory arrest No autopsy (suspected diagnosis of T-E fistula without atresia)	40	—
7.	1431	30 weeks	None	Bradycardia followed by cardiac arrest Autopsy: 1. Hemorrhage into the brain stem and ventricles	1	—

TABLE II

PREMATURE INFANTS WITH RESPIRATORY DISTRESS REQUIRING EARLY USE OF A RESPIRATOR

Case	Birth Weight (gm)	Estimated Gestational Age	Early Complications	Complications After Beginning Hyperalimentation	Days of Hyper-alimentation	Discharge Weight (gm)
8.	1191	28 weeks	Apgar = 6 at one minute followed by cyanosis, flaccidity, and absence of spontaneous respirations, requiring a respirator Hyaline membrane disease Precipitous delivery in bed Septicemia at birth	Progressive hyaline membrane disease Poor perfusion, renal failure and arrest Autopsy: 1. Severe hyaline membrane disease 2. Massive bilateral intraventricular hemorrhage and brain stem compression	6	—
9.	1134	28 weeks	Caesarian section because of transverse lie 12 hours after rupture of membranes Bruising of head Respiratory arrest requiring a respirator	Inadequate pulmonary exchange Neurologic depression Cardiac arrest. Autopsy: 1. Intraventricular hemorrhage and midbrain hemorrhage 2. Hyaline membrane disease	4	—
10.	1191	28 weeks	Cord prolapse five minutes prior to delivery and cord nonpulsatile Spontaneous respiration followed by apnea and bradycardia requiring a respirator	Inability to maintain adequate blood gases requiring a respirator Cardiac arrest Autopsy: 1. Hyaline membrane disease 2. Acute ventricular and midbrain hemorrhage	1	—

Fig. 1—Case #1. The baby weighed 964 gm at birth and gradually lost weight on conventional management until he weighed only 640 gm.

Case 1: Q.N., a 964-gm male, was born to a 20-year-old *gravida* I, *para* 0, *abortus* 0 female on 7-26-70 with an expected date of confinement of 10-22-70. (Figure 1). The gestational age was estimated to be 28 weeks. The Apgar score was 4 at 1 minute and 9 at 5 minutes. The infant had early respiratory distress and several documented episodes of sepsis during the early weeks of life. In spite of gavage feedings, by 8-13-70 the infant was quite lethargic and weak, with frequent apnea, and he weighed only 640 gm. The child was then started on hyperalimentation, with a gradual rise in weight until 9-3-70 when the catheter was found to be obstructed with a precipitate of calcium carbonate. The child had obtained a weight of 1120 gm by this time and was tolerating oral feedings well, so it was elected to manage the child with oral feedings alone. The child was discharged on 10-15-70 with a weight of 2098 gm, and was continuing to do well when lost to follow up about one month after discharge. Initially, there were some problems with hyperglycemia and metabolic acidosis, but these were easily controlled by altering the composition of the infusate and giving small amounts of insulin for a few days until the infant was able to tolerate the dextrose.

Comment: Calcium is no longer added to the solution since, in the presence of sodium bicarbonate, a precipitate of calcium carbonate forms which may obstruct the central venous catheter.

Case 4: T.W., a 1729 gm male, was born to a 22-year-old *gravida* 2, *para* I, *abortus* 0 female on 9-8-70 with an expected date of confinement of 10-25-70. The gestational age was estimated at 32 weeks. The infant had moderate respiratory distress. Hyperalimentation was started on 9-12-70. The child was discharged on 9-29-70 with a weight of 2268 gm after 14 days of hyperalimentation. There were no complications.

Comment: This case demonstrates that with early respiratory distress the initial weight loss can be significantly reduced and adequate protein and calories can be supplied without distending the stomach and increasing the respiratory distress.

Case 5: J.W., a 1332-gm male identical twin, was born to a 25-year-old *gravida* 5, *para* 4, *abortus* 0 female on 9-11-70 with an expected date of confinement of 12-4-70. The gestational age was estimated at 28 weeks. Hyperalimentation was started on 9-17-70. The child gained weight but intermittently required insulin in amounts up to 1.6 units to control hyperglycemia. On 9-23-70 the neck wound was noted to be infected. Cultures of the wound grew out coagulase positive Staphylococcus. The wound was treated with drainage, warm moist packs, and antibiotics. On 9-24-70 the infant aspirated a large amount of formula and had a cardiorespiratory arrest. Resuscitation was successful, but the child continued to lose weight for four days until he weighed 1176 gm. However, the child continued to show a significantly positive nitrogen balance, and, after the initial weight loss, gained weight rapidly (Figure 2). The catheter was removed on 10-8-70 because of a blood culture which was positive for coagulase positive Staphylococcus. As the catheter was removed, purulent material was noted just beneath the scalp wound which on culture was

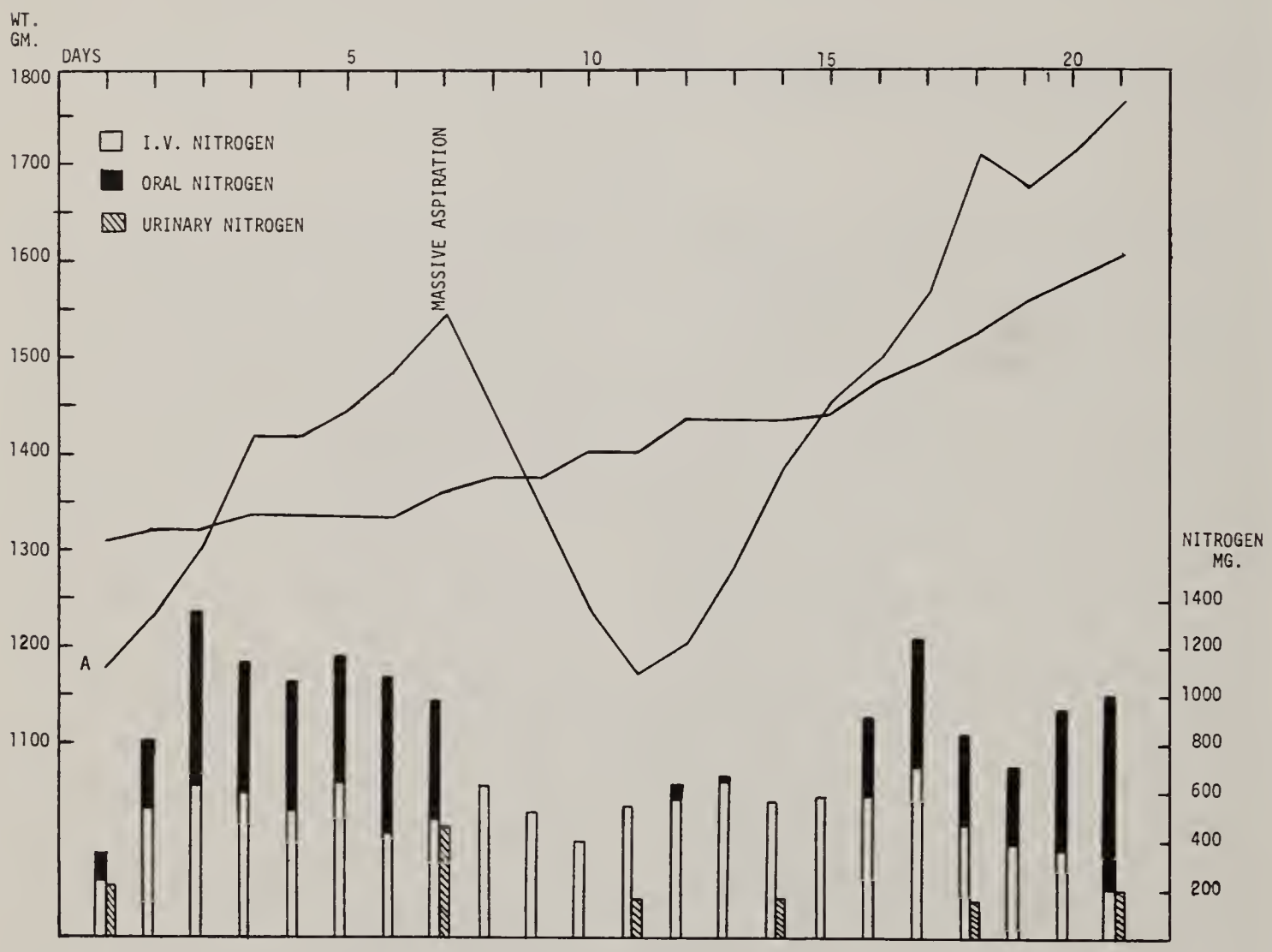

Fig. 2—Comparison of weight curves of identical twins. A—Hyperalimented. B—Conventional oral feeding (Enfamil 27 Cal/oz).

found to contain *Candida albicans*. The scalp wound was treated with topical nystatin. The child weighed 1772 gm at the time of catheter removal and was continued on oral feedings. He was discharged on 10-30-70 at a weight of 2041 gm. He has continued to do well and at 30 weeks of age weighed 5854 gm; his height and head circumference were at the 25th percentile.

Comment: This case illustrates several points. Prolonged hyperglycemia or hyperglycemia occurring in a previously stable infant on hyperalimentation suggests the possibility of infection. Figure 1 compares the weight curve of this infant with his larger identical twin, who was treated with conventional oral feedings of Enfamil* (27 Cal/oz). The hyperalimented twin gained weight much more rapidly. The stress of the massive aspiration and arrest caused a sharp fall in weight even though the infant continued to receive protein and calories from the hyperalimentation solution. It is doubtful that the infant could have survived the stress of the massive aspiration without the calories and protein which the hyperalimentation solution continued to supply him.

Case 8: Y.C., a 1191-gm male twin, was born precipitously in bed to a 21-year-old *gravida* 6, *para* 3, *abortus* 2 female with an expected date of confinement of 11-24-70. The gestational age was estimated to be 28 weeks. At one minute the Apgar score was 6, but the child rapidly became cyanotic and flaccic with no spontaneous respirations. He was placed on a respirator. On 10-12-70 hyperalimentation was started. Chest x-rays showed progressive hyaline membrane disease, and the child had a progressive downhill course leading to poor perfusion, renal failure, and arrest on 10-18-70. Autopsy revealed severe hyaline membrane disease, massive bilateral intraventricular hemorrhage with brain stem compression, and thrombosis of the transverse sinus.

Comment: This case demonstrates that with early respiratory distress severe enough to require the use of a respirator, the infant is unlikely to be salvagable by hyperalimentation.

MATERIALS AND METHODS

The hyperalimentation solution is administered at a slow, uniform rate to insure proper utilization and is infused into an area of high blood flow so that there will be a rapid dilution in order to avoid venous inflammation and thrombosis. In the operating room, using sterile technique, a silastic catheter (inner diameter of 0.025 inches and an outer diameter of 0.047 inches) which has been impregnated with silver to make it radiopaque[a] is introduced into the external or internal jugular vein and advanced down into the superior vena cava using the method of Wilmore and Dudrick.[14,15] The silastic catheter is then attached to a 21-gauge butterfly needle[b] which has been broken off to make a blunt cannula. A short segment of larger silastic tubing is placed as a sleeve around the needle. The butterfly needle can be taped firmly to the head, and this may explain our failure to have any catheters accidently dislodged, even though one catheter was used for 75 days in another baby hyperalimented by the authors. The silastic sleeve prevents kinking of the tubing at the needle (See Figure 3.)

The solution is administered at a slow, constant rate by means of a roller pump[c] and passes through a millipore filter[d] to

*Enfamil, Mead Johnson

a. Silastic catheter impregnated by silver, Extracorporeal Medical Specialties, Inc., Mount Laurel Twp., N.J. 08057
b. Butterfly needle, Abbott Laboratories, North Chicago, Ill.
c. 900 Series Holter Pump, Extracorporeal Medical Specialties, Inc., Mount Laurel Twp., N.J. 08057
d. 9200 Series I.V. Pump Set Filter, Extracorporeal Medical Specialties, Inc., Mount Laurel Twp., N.J. 08057

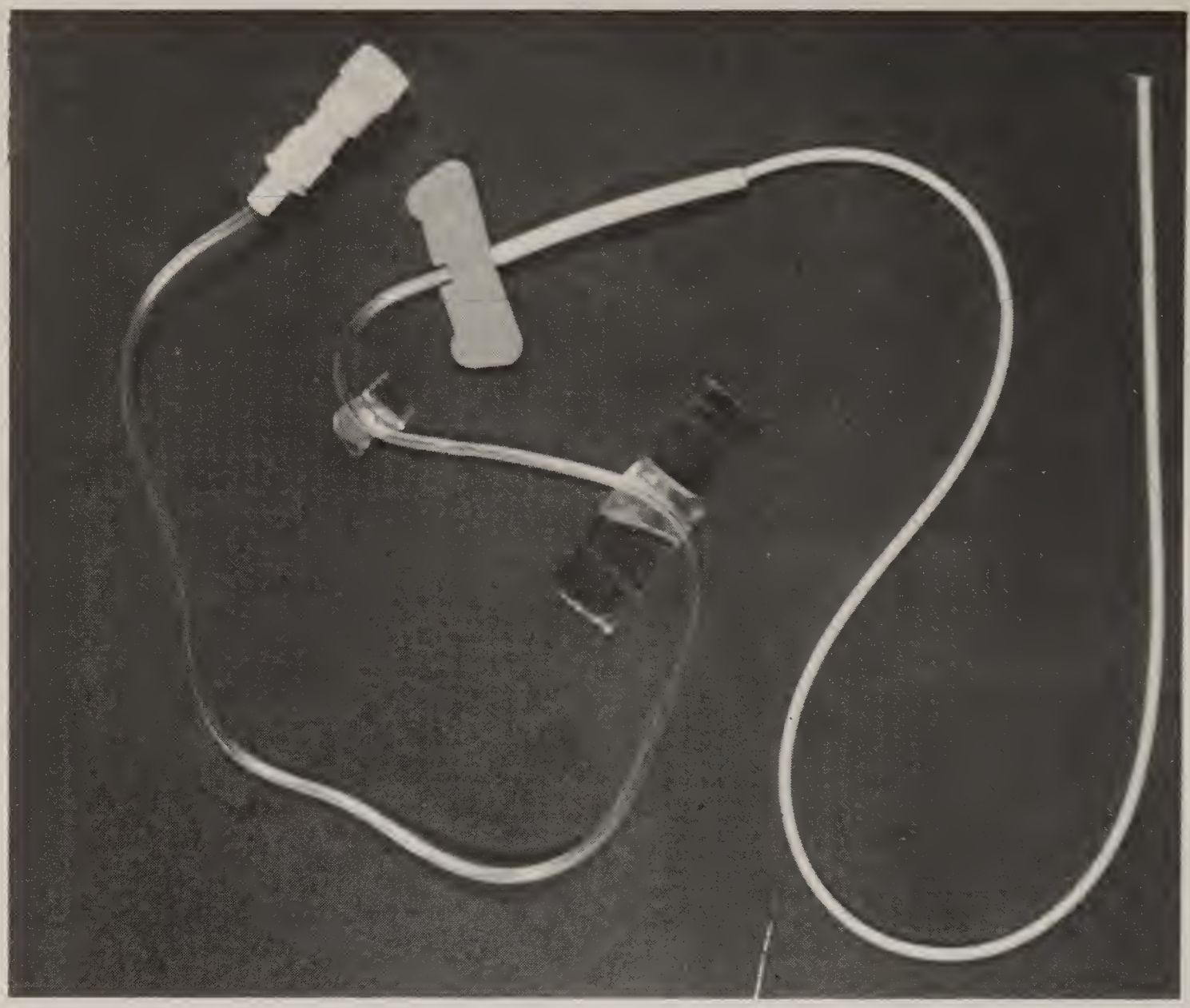

Fig. 3—Catheter used for hyperalimentation. Butterfly infusion set may be firmly attached to the head and may help to explain the failure to have any catheter dislodgement in the present series.

remove particulate matter and microorganisms. The hyperalimentation solution is prepared in the hospital pharmacy under a laminar flow hood. The hyperalimentation bottle is connected to a Buretrol[e] chamber for accurate measurement of the volumes infused and also to a Pediatrol[f] which insures against air embolism.

The hyperalimentation solution contains:

5 percent Synthetic Aminisol[g]	65 ml*
40 percent dextrose in water[g]	55 ml*
Potassium phosphate (3 mEq/ml)	0.2 ml
Sodium bicarbonate	5 ml
50 percent Magnesium sulfate	0.125 ml
Vi-Syneral[h]	0.25 ml/24 hours
Heparin	50 units

e. Buretrol, Travenol Laboratories, Inc., Morton Grove, Ill.
f. Pediatrol, Travenol Laboratories, Inc., Morton Grove, Ill.
g. Aminosol Kit, Abbott Laboratories, North Chicago, Ill. (Supplied as experimental drug by Abbott Laboratories, Inc.)
h. Vi-Syneral, USU Pharmaceutical Corp., Tuckahoe, N.Y. 10707

* Solution presently unavailable; replaced by 50 percent Amigen in 5 percent dextrose in water—75 ml (Abbott Laboratories, North Chicago, Ill.) 50 percent dextrose in water—45 ml.
When this solution is used sodium is replaced as 5 percent NaCl 2 ml/kg.

Seventy-five ml of 5 percent Amigen (in 5 percent dextrose in water and 45 ml 50 percent dextrose in water may be substituted for the Aminosol Kit. This solution supplies the approximate requirements per kg and contains 3.25 gm of protein and 22 gm of carbohydrate (88 calories). The solution exceeds the minimal daily requirement of amino acids as illustrated by Figure 4. The 5 percent Synthetic Aminosol contains all 1-amino acids, but does require 1 ml of sodium bicarbonate for each 11 ml of Aminosol in order to prevent a metabolic acidosis. The sodium has been well tolerated in all but one infant (Case 6) in whom there was a transient pre-renal azotemia. The sodium carbonate is not required when the Amigen is used.

During the first twenty-four hours of

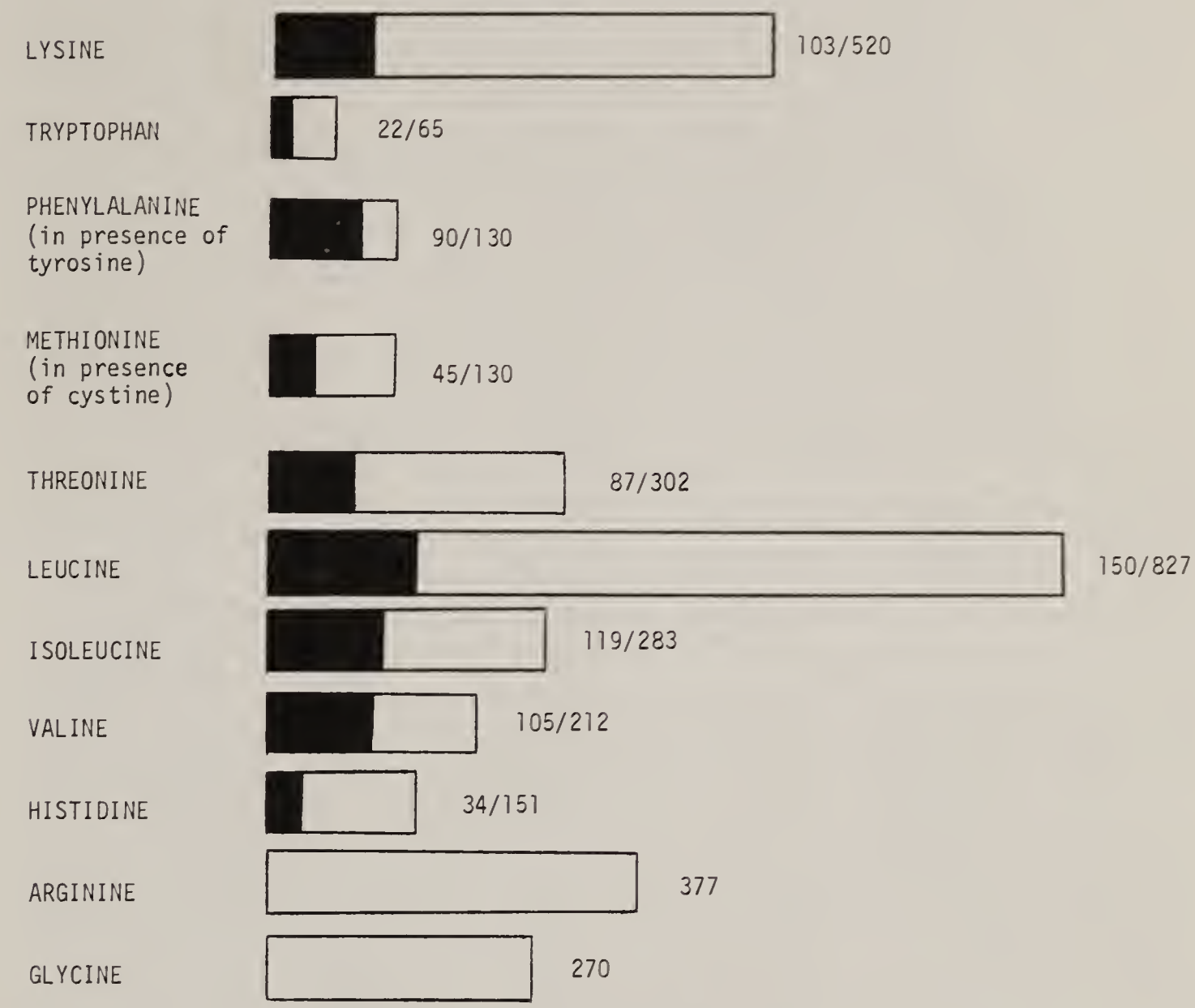

Fig. 4

hyperalimentation, the hyperalimentation solution is administered at a rate of 80 ml per kg. The volume of fluid is gradually increased until the infant is receiving 120 ml per kg. The infant rapidly becomes able to handle the glucose load, and can tolerate 120 cc/ml kg of the fluid within three or four days. The infant is simultaneously offered formula containing 27 calories per ounce every three hours and allowed to take as much as he drinks readily, up to 30 ml.

No attempt has been made to supply fatty acids and trace elements parenterally since these should be supplied by the oral formula. Calcium is supplied orally as Neo-Calglucon.[i]

Due to the small blood volumes of the infants, the measurement of blood chemistries is held to a minimum. Serum glutamic pyruvic transaminase (SGPT), bilirubin, and blood urea nitrogen (BUN) are determined weekly. In the present series of infants there has been only one elevated BUN, which was transient and returned to normal after the concentration of the solution was decreased for three days. This occurred in the only infant in the series who required an exchange transfusion for hyperbilirubinemia (Case 6), and may have been in some way related to this. Every voided urine specimen is checked for pH and sugar. Initially, most of the infants have glycosuria which has in all cases thus far been limited to the first five days except for Case 5 in which there was a wound infection. The infants have a very low renal threshold for sugar, and some of the infants have had glycosuria with a blood sugar of only 50 to 60 mg. per 100 ml. When an infant has 4+ glycosuria, a blood sugar determination is done, and the infant is treated with insulin if indicated by an elevated blood sugar (over 175 mg. per 100 ml).

The intravenous tubing and the wound require meticulous care. The filter is changed every 48 hours. The tubing is changed and the wound redressed with ether, iodine, and alcohol followed by the application of Betadine ointment[j] every 96 hours. These procedures are done using strict sterile technique with cap, mask, and gloves. The hyperalimentation solution is prepared each morning, and no bottle is allowed to remain hanging over 24 hours.

No drugs or blood are administered through the hyperalimentation catheter, and the catheter is never used for drawing blood.

DISCUSSION

The ten premature infants treated with hyperalimentation may be divided into two groups. Cases 1 to 7 were infants not requiring a respirator prior to hyperalimentation. Of these seven infants, five have rapidly gained weight and done well with continued weight gain after the discontinuation of hyperalimentation. (Figure 5). It has been stated that optimal intrauterine weight gain is in the range of 24 to 40 gm per day.[12] The premature infants in this series have usually exceeded this amount of weight gain, and weight gains up to 140 gm per day have been achieved. The weight gains have also exceeded those outlined by Dancis, O'Connell and Holt for premature infants without complications[16] (Figures 6 and 7). Two infants have expired, one with brain stem hemorrhage and one with massive aspiration, for a mortality of 28.5 percent in the group of premature infants who did not have respiratory distress prior to hyperalimentation sufficient to require the use of a respirator.

Cases 8 to 10 were infants with respiratory distress requiring the use of a respirator early in life. All three infants in this group expired. The causes of

i. Neo-Calglucon (Glubionate calcium), Sandoz Pharmaceuticals, Hanover, N.J. 07936

j. Betadine Ointment (Povidone-iodine), Purdue-Frederick Company, Yonkers, N.Y. 10701

Fig. 5—Case #3. This baby weighed 1183 gm at birth. At seven months the infant weighed 6570 gm.

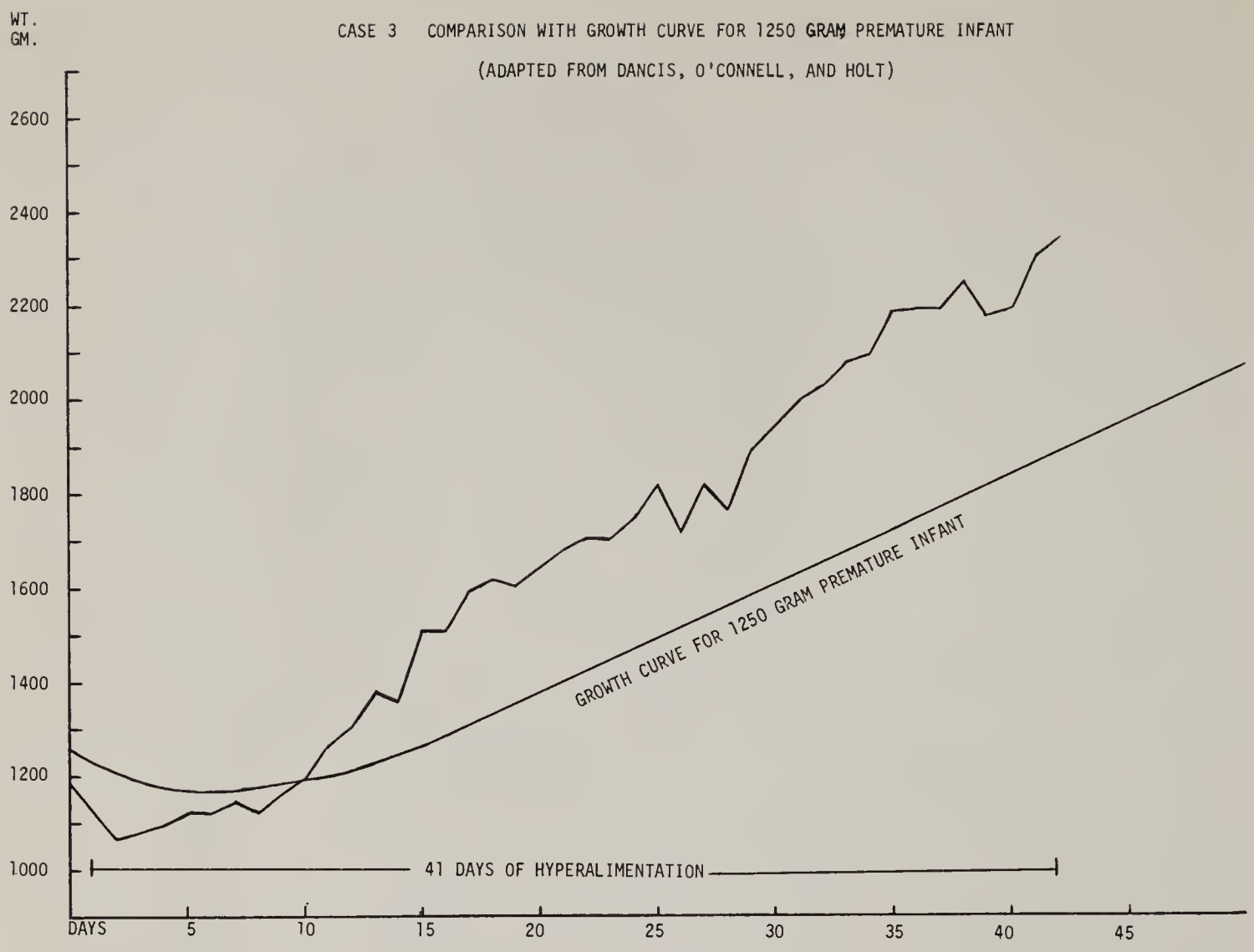

Fig. 6

death were severe hyaline membrane disease in one infant and brain stem hemorrhage in the other two infants.

One infant developed a wound infection with staphylococcus and *Candida albicans* which responded to removal of the catheter and topical nystatin. All of the other catheters have been sterile at the time of removal.

The only other complications of hyperalimentation have been hyperglycemia and metabolic acidosis. The hyperglycemia has been transient and has been easily treated with small amounts of insulin when it has occurred. The metabolic acidosis occurred early in the series when the best composition of the hyperalimentation solution was being determined. Other complications which have been reported with hyperalimentation are obstruction of major vessels, severe dehydration secondary to an osmotic diueresis, extravasation of fluid, and catheter dislodgement.[17] None of these complications has occurred in the present series.

The high incidence of brain stem hemorrhage has corresponded to other series. Seventy-five percent of the babies in this series who were found to have brain stem hemorrhage at autopsy had early respiratory difficulty requiring the use of a respirator. Valdes-Dapena and Arey have reported a mortality of 91 percent in infants born with a birth weight of 1000 gm or less. The primary causes of death in these infants as confirmed by autopsy were intraventricular hemorrhage (34 percent), inflammatory lesions (26 percent), pulmonary hyaline membrane disease (23 percent), and immaturity with a weight less than 500 gm

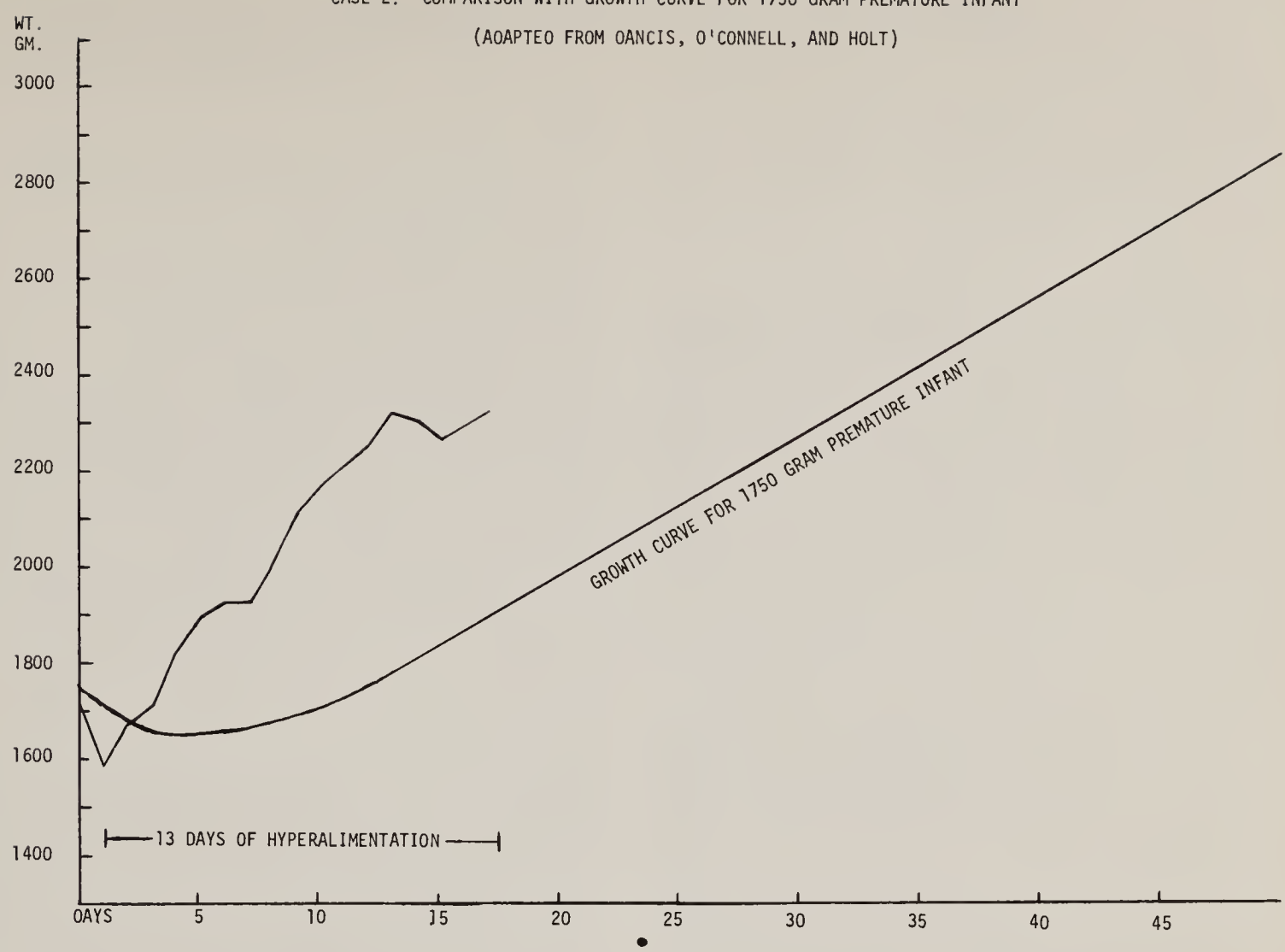

Fig. 7

(19 percent).[18] Hathaway has reported that approximately 40 percent of deaths in the nursery have associated hemorrhage or thromboses described at autopsy.[19] Cade, Hirsch, and Martin have indicated that coagulation factors (except fibrinogen) were significantly lower in 1000-gm premature infants than in full term or larger premature infants.[19] Aballi has described increased capillary fragility and prolonged bleeding times in small premature infants. Recent reports of altered platelet function in the newborn have suggested that these "capillary fragility" changes are due to a qualitative defect in the platelet.[19]

CONCLUSION

Hyperalimentation appears to help in the management of the premature infant whose oral intake supplies inadequate protein and calories for maximal growth. This includes essentially all infants of less than 1000 gm and most infants of less than 1500 gm. It is especially beneficial in the infant with respiratory distress, since it allows adequate nutrition without gastric distension which further compensates the respiratory reserve. In addition, these infants are easily fatigued by eating, and aspiration is common. The hyperalimentation solution supplied calories and protein which may help the infant survive the stress of a catastrophe such as massive aspiration (Case 5). Hyperalimentation appears to be unlikely to aid in the salvage of infants with respiratory distress during early life sufficient to require a respirator to maintain life.

SUMMARY

Hyperalimentation has been studied in a series of 10 premature infants. Complications due to hyperalimentation have been minimal, and there has been no mortality attributable to the hyperalimentation.

By the use of hyperalimentation to supplement oral feedings, the infants have had a greater propensity toward a significantly positive nitrogen balance and appear to have gained strength more rapidly and required shorter periods of hospitalization with their inherent risk of exposure to infection from resistant organisms. The need for large oral feedings with the risk of aspiration and the impairment of respiration due to gastric distension have likewise been avoided.

In a short followup period the infants compare favorably in growth and motor development with normal-term babies of the same age.

The preliminary result in this small series has impressed the authors that the technique is helpful in the management of the premature infant. It merits further investigation.

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PERSONALITY DEVELOPMENT AS ILLUSTRATED BY THE MEDEA

Richard Koenig

The objective of this article is to illustrate the drama and complexities of personality development by viewing The Medea as an allegory depicting in a social setting what is happening in the psychic world of mental representations, drives, and drive control. As in all allegories, efforts to draw parallels fail at the rational level, and the intention is merely to nudge the reader's imagination rather than outline as real something that is basically abstract.

The Medea, by Euripedes, can be viewed first as a play about a woman who murders to express her passions; and, secondly as a dramatization of psychic structure-formation necessary for personality development. The former can be seen as a regressive attempt to adapt to the absence of psychic structure, notably superego and post-oedipal ego ideal.

The thesis here would be that disillusioning frustration (mortification) is necessary for normal personality development in that if it is not excessive, it induces internalizations via the mourning process. Failure in establishing such drive-regulating internalizations permits the acting out of wishes to abolish the displeasure, experienced with mortification, through suicide and/or murder.

In the play, the barbarian Princess Medea not only commits filicide, but murders her brother in order to flee with her Greek lover, Jason. She tricks the daughters of Pelias into dismembering their father (with the promise he can thus be rejuvenated) in order to revenge Jason. Again Medea and Jason have to flee. When Jason "deserts" Medea for the daughter of Creon, the king of Corinth, Medea arranges the death of Creon and his daughter, then kills her children in order to hurt Jason and to prevent anyone else from getting revenge on them. Finally she escapes by supernatural means to take refuge with old King Aegeus, whom she has promised to aid in his childlessness in return for his protection.

When the nurse observes early in the play that "love is diseased—she is a strange woman;" the idea is expressed that Medea is either fixated or regressed, or both. The tutor gives voice to the nature of the problem, a narcissistic vulnerability compounded by necessary object losses: "Old ties give place to new ones—everyone loves himself more than neighbors." Medea voices her distress; "I wish . . . I wish I might die. I hate you, children of a hateful mother. I wish the lightning would split my head open. O, my father, in what dishonor I left you." Here Medea expresses her failure in neutralizing her sibling rage at mother for having other loves, and her oedipal rage at father for the same fact. Thus, her children are subjectively conceived in dishonor and competition with

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the parents, rather than in resulting from an "honorable" identification. They remind her of her frustration, rather than satisfy her appropriate neutralized wishes. The only relief for such murderous wishes is death (or repression), which she calls forth upon herself. The nurse expresses this well when she says, "bitter grief from which death and disaster cheat the hopes of a house." Grief is only bitter when it cannot be resolved. Successful mourning turns grief to sweet hopes for new beginnings.

In saying, "it was everything to me to think well of one man," Medea conveys the idea that Jason represented something that was lacking in herself, rather than an object for her postoedipal love. She goes on to confirm this by exclaiming; "I have no mother or brother nor any relation with whom I can take refuge." Creon gives voice to the omnipotent controlling "self-object" that is motivated by the principal, "what is pleasurable is me; what is unpleasurable is not me," when he says, "I order you to leave my territories." When Medea replies, "for myself I do not mind if I go into exile. It is the children being in trouble that I mind," she is showing evidence of a struggle to accept the reality principle and give up her omnipotent and incestuous wishes. The chorus puts forth this developmental dilemma with the following: "Flow backwards to your sources, sacred rivers." The need for narcissistic cathexes to be reinternalized on newly developed capacities for motherliness is clearly indicated. It goes on to say, "you have lost your rest in a widowed bed and are driven forth a refugee." Thus, the reality of frustration demands more than rage, including the courage and capacity of a refugee in a new land. Each of the various lands in which Medea sojourns represents a newer, more complicated phase of personality development. The barbarian homeland on the other side of the Black Sea represents experiences in the poorly differentiated, blissful-raging state of pre-object-constancy. The land where she and Jason first settle represents the ambivalent state of pre-oedipal incorporations and projections of the phallic mother. Corinth, the scene of the play, represents the oedipal state of love where all is fair, and rejection and disillusionment turn to wars of revenge. Athens, the land to which Medea escapes, represents the post-oedipal state of object related creativity, where husband wife and child are all objectified and only secondarily cathected with narcissistic aims.

Jason encourages Medea to remain fixated at an oedipal level when he advises, "with reasonable submission to our ruler's will, you might have lived in this land. Exile brings with it many troubles." Medea rejects the idea of submission, calling it shamelessness: "Yours is the worst of all human diseases, shamelessness." Jason's response is to wish oedipal conflicts could be avoided, when he says, "it would have been better for man to have gotten their children in some other way and woman not to have existed." Here, the chorus injects a bit of reality-judgment. "You have betrayed your wife and are acting badly." Medea then, thinking about her future, asks for the impossible. "Let me have no happy fortune that brings pain with it." Aegeus, who is to be Medea's future husband, then comes on the scene to inquire how children might be born to him, and Medea promises to end his childlessness. Aegeus agrees to this with the provision she will have to make her escape "from this land" on her own. Thus, until she has resolved her oedipal conflict, she will not be available to him, nor he to her. Medea insists that Aegeus "swear by the plain of earth that you will never yourself cast me from your land," adding, "I will reach your city as soon as I can, having done the deed I have to do"—that is, giving up her wish for children that represent a defiance of incestuous morality. The chorus is torn, wanting Medea to go forward, and remain fixated at the same time. "I both wish to help you, and support the normal way of mankind and tell you not to do this thing." Resignedly Medea says, "so it

must be; no compromise is possible." She goes on to say, "they were sterile, those pains I had in the bearing of you. Come children, I wish you happiness, but not here in this world."

The messenger announces the death of Creon's daughter, saying, "she opened her shut and speechless eye. She was hard to be recognized except by a parent. There they lie close, the daughter and the old father." This represents the death of Medea's Oedipal strivings—her speechless eye cannot tell her of the father's nearness. When Jason hears of his children's death, he says, "O woman, you have destroyed me." Again, Jason represents the "rejected" oedipal object who must be hurt, the basic tragedy of civilization. Jason complains, "I took you from your foreign home . . . you, an evil thing, a traitress to your father and native land . . . your own brother you slew at your hearth side and then came aboard that beautiful ship, the Argo." Medea replies, as though justifying her heartlessness, "it was not to be that you scorn my love and pleasantly live your life through, laughing at me." Her new orientation to the future is next expressed with, "I shall establish a holy feast and sacrifice each year forever to atone for the blood guilt."

The chorus concludes the play with an attempt to explain the grisly happenings. "Many things the gods achieve beyond our judgment." Thus, although we all hate frustration and conflict, these are the stuff of which progress is made. Finally, the chorus gives voice to the limitations of human consciousness, and the many paradoxes to which reason leads: "What we thought is not confirmed, and what we thought not, God contrives. And so it happens in this story." We might add, and so it happens in personality development.

Glossary

Fixated: Undeveloped, lacking in phase appropriate internalizations

Incorporations: Object representations (experiences) that are confused with self-experiences

Internalizations: Learned ego capacities

Narcissistic: Self-interests

Narcissistic aims: Striving for perfection, a constant state of equilibrium, etc.

"Narcissistic cathexis": The experience (subjective) of self-interests

Oedipal: Transitional self, seeking both completion and fulfillment

"Phallic" mother: A mental creation designed to give the illusion of completion to the "incomplete" immature self

Post-oedipal: Mature self, seeking fulfillment more than completion

Pre-oedipal: Immature self, seeking completion more than fulfillment

Pre-object-constancy: Before the psyche has the capacity to fantasize the object in the face of frustration by (loss of) the object

Projections: Self-experiences that are perceived as external to the self

Regressed: "De-developed," loss of phase appropriate internalizations

Reinternalized: Relearned (modified) ego capacity

"Self-object": Narcissistic experience of undifferentiated self and object as omnipotent

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CHICAGO: PATIENTS AND PROVIDERS, OR WHO TAKES CARE OF WHOM?

Irene R. Turner

Adequate health care means that there is a sufficient volume of good medical and other health services to meet the needs of a community in accord with the ever-changing and advancing standards of medical and health practices. Traditionally, health care has been provided by a multiplicity of groups, taking diverse directions. Our health care system has been described as a cottage industry in a highly-organized society. It is more and more frequently described as a non-system. This non-system has continued to exist despite the influences of science and technology and the tremendous expenditures for health care in the United States.

The base of the system has been the office of the family physician. This traditional form has been changing in recent decades but it has been changing largely as a result of circumstances, rather than from rational planning to meet the changing times. Availability of techniques for treatment of acute, reversible and, often formerly fatal, disease has shifted much of the activity from the doctor's office to hospitals and medical centers. This shift has carried with it a major share of the personnel involved and also a substantial portion of the financing. As the population and its knowledge of health problems continues to expand, the demands for care increase in geometric proportion. However, availability and quality of care have not kept pace. Some of the deficits in the availability of health care for all segments of the population were quantified in a survey undertaken by the University of Illinois Survey Research Laboratory for the Campbell group study of education in the health fields in 1967-68.[1]

In this survey it was found that eleven percent of adults and nine percent of children in Illinois had no regular source of medical care. This was a state-wide average but the deficits in the southern tier of the state and the densely populated inner city of Chicago were greater than the average. Twenty-six percent of the adults and 19 percent of the children in Illinois had no access to, or had not availed themselves of, adequate preventive services as judged by the fact that they had not undergone a complete physical examination in the five years preceding the survey. (As an aside, it may be of interest to observe that for those who had had a complete physical examination in the preceding five years, the thoroughness of the examinations left something to be desired. In less than half were the patient's feet examined or was there any rectal examination or was the patient asked to undress completely. For 42 percent of the women, no pelvic examination was performed, while a "Pap" smear was taken in only 50 percent of female examinations which did include the pelvic examination.

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The situation relative to dental care was even less favorable. One-third of the adult respondents in the survey did not have a regular source of dental care, nor did one-third of the children. This deficit was worse in black respondents: 40 percent of the non-white respondents indicated that they had no regular source of dental care as compared with 23 percent of the white respondents. Economic factors played a role, as would be expected. Fifty-seven percent of the families with income under $4,000.00 per year did not have a regular source of dental care for their children.[1]

Chicago also enjoys the dubious distinction of leading the large cities of the nation in its black infant mortality rate. The total infant mortality rate in the city worsened between 1963 and 1969, rising from a rate of 27.5 per 1,000 live births in 1963 to 29.5 in 1969, while in the United States and the state of Illinois total infant death rates were declining.[2,3] This not only implies a lack of adequate health care, but in this city, as in most major cities in the United States, there is a dual health care system, one for white and one for black. There are estimated to be approximately 1,000,000 poor or near-poor people in Chicago, and many are black. If one isolates this population, it would comprise the sixth largest city in the United States, so let us examine in detail the health care system as it applies to this sixth largest city. This is not to imply that the other system for the white and affluent is much better. When such people become ill, they simply lift the phone and call their private doctor who then takes over, sees them in his office, runs the appropriate tests (hopefully), hospitalizes them if necessary, arranges for consultations that are indicated, and follows their course after discharge. When they are well again, he suggests they come in for a regular physical examination and they have access to preventive and detection programs that may help keep them healthy.

Such is not the case for the poor. The poverty-patient frequently does not even have a phone he can lift to call a private doctor if he knew a doctor to call. The paucity of physicians in the poverty areas is another factor which militates against access to private medical care. Thus, the patient usually gets on a bus and heads for an emergency room. In Chicago, often as not, that emergency room is in Cook County Hospital which may be many miles from his home. If he knows of an out-patient clinic elsewhere, he may present there, but there are only a limited number of out-patient clinics in this city, and that number is even more limited if one happens to be black. The large out-patient departments serving poor people usually are located in teaching hospitals where there are criteria for acceptance of patients, and the patient may not meet those criteria. Thus, the patient may be "seen and advised" in the emergency room (or screening area), treated for his immediate complaint, sent home, and advised to return only if he becomes ill again. If the patient is fortunate enough to be accepted for comprehensive care he may then be subjected to a common out-patient clinic procedure such as seeing a different doctor on each visit. If he needs hospitalization, he may be seen by still a different doctor in the house, and when discharged and returned to the clinic for follow-up may be seen by yet another doctor. On occasion, his chart has been lost and he must wait hours until it is located. When the chart is found, the new physician still may possess only fragmentary, incomplete and often illegible notes as to his patient's course. Because of the differences in cultural and social backgrounds between doctor and patient, communication necessary to optimal management of the patient may be lacking or inadequate.

It is true that some changes have been effected in this situation. In the interest of providing continuity of health care, at Rush-Presbyterian-St. Luke's Medical Center patients are assigned to a specific doctor for both ambulatory and inpatient care. There is an appointment system, and some of the amenities are offered. At Cook County's Fantus Clinic

they are trying to bring these amenities to their clinics. But major and glaring lacks still exist in all out-patient clinics which perhaps will not be remedied until the entire dual care system, or mentality, is changed. In recent years, the depersonalization attending clinic and emergency room care, its overall inadequacy and indignity, have been felt more keenly by the patients. This has contributed to a great upsurge of verbalized anger against the whole health care system and its providers. These patients see themselves as victims, rather than beneficiaries of the system, and not without justification.

Other forms of ambulatory services available to this population are also fragmented and lack continuity. In Chicago, major dispensers of those services include the Board of Health, the Board of Education, the Division of Mental Health and the Department of Public Aid. While the latter does not provide services itself, it pays for services and is thus an integral part of the delivery system. Time is limited and more complete information is available on the nature and types of these services in the Lepper-Lashof report.[4] Suffice it to say that the Board of Health maintains about 35 infant welfare stations, 18 pre-natal clinics, 6 family planning units, 2 venereal disease centers, and 2 adult diagnostic screening centers. Limited nursing services and some physicians are available to do a small number of physical examinations in the schools. The Board of Health has recently opened two comprehensive care centers. Other neighborhood health centers are on their drawing boards.

The Division of Mental Health provides some diagnostic services, individual and group psychotherapy, and plays a limited consultative and collaborative role *vis-a-vis* the schools, churches, police agencies, local community groups and public aid workers. As an example, however, of the paucity of these services, there were in recent years 14,000 school children on waiting lists for psychological evaluation. The schools do provide good vision and hearing testing programs, some physical and dental examinations, and minimal detection programs for cardiac disease, epilepsy, mental retardation, mental health and tuberculosis.

The desperately needed nursing home type of facility and service is totally unrelated to systematic delivery of health care. In recent years, governance of these homes has shifted from 60 percent voluntary to 92 percent proprietary ownership nationally. Only seven percent of their total admissions nationally were of black patients and 90 percent of this small number were supported by public funds.

This is a brief over-view of the types and nature of the services available to the poor patient.

The three major building blocks of the health care system must be examined to see how they affect care to the poor. They are manpower, facilities, and financing. Let us look at manpower first, especially physician manpower. Other health manpower is equally important but the shortage and maldistribution of physicians is the most dramatic problem. Manpower-to-population ratios are rudimentary measures of physicians' availability but they are traditionally used and for lack of a better tool, I will use them too, recognizing the limitations. In the Chicago Standard Metropolitan Statistical Area (S.M.S.A.) with a population of just under 7,000,000 people, there are 11,575 physicians. This ratio of 1.7 physicians for 1,000 population is more favorable than the national ratio of 1.45 per 1,000. It appears favorable until one examines the situation in more detail. Of the 11,575 physicians, only 9,825 are in private practice and of that number only 6,552 have practices where patients may seek primary care or be referred. The remainder are in medical teaching, administration, research and—the ubiquitous—"other." This leaves a ratio of 0.9 of a physician per 1,000 persons.

But there is still another key question which must be examined relative to availability of physician manpower, and that is the geographic distribution within the S.M.S.A. DeVise[5] has pointed out in his work that there has been a marked physician exodus from the city of Chicago

to the suburban areas. He estimates that there are 2,000 fewer physicians practicing in Chicago now than there were in the early thirties. This is exacerbated in the poverty communities as reported by Lepper and Lashof[4] who found that there were half as many physicians practicing in poverty areas as compared with non-poverty communities and the disparity became greater for specialty practice. Further examples are cited by DeVise.[5] He points out that there were 212 physicians practicing in East Garfield Park in 1930 compared to about a dozen now. There are more than 50,000 residents in that area which is a ratio of about 0.2 of a physician per 1,000 population. In Kenwood-Oakland on the South Side, there are now five physicians serving about 44,000 people as compared with 110 serving 28,000 when the community was all white 30 years ago. This is a ratio of about 0.1 of a physician per 1,000 people.

A shortage of physicians is found in non-poverty areas as well. The Southwest Side of Chicago suffers a physician shortage and also a shortage of hospital and ambulatory care facilities. Substantial numbers of the population there are blue-collar workers who have sources of funding through their employment or union affiliations but only have limited access to health care.The physician there, usually of the same ethnic background, tends to be aging and unwilling or unable to expand his practice; indeed, he is usually seeking to contract it. He is not being replaced by younger physicians in numbers sufficient to meet the needs.

The physician exodus from the city is, in large part, dictated by financial criteria. The physician can afford a home in a suburb and prefers to live there for many reasons. Traditionally, physicians have located their practices relatively near their homes so that their very expensive time is not consumed in traveling. Also, poor communities have no financial base. The fees patients can pay, or welfare will pay, are low and the physician must see a large volume of patients in order to earn the income he desires.

There must be some mention of the black physician. In Chicago, there are approximately 240 black physicians. There have been between 230 and 238 since the early 1900's, so it is evident that this city has not attracted black doctors. It is true that the entire number of black physicians in the nation has been microscopic and the Illinois medical schools have not had more than a dozen or 15 black students enrolled in all of them each year for at least 20 years until recently. However, this has been only one of the factors which has created the scarcity of black physicians in Chicago. Until a dozen or so years ago, black physicians were discriminated against in hospital staff appointments, though a legal suit by nine black doctors in 1958 changed this situation. The present black doctor group is an aging one, and the last study I remember on this subject showed the median age to be in the 50's. Black physicians are approximately two percent of the total physician population in Chicago while the black resident population, to whom they primarily relate, is 35 percent.

As stated earlier, the scarcity of physicians in poverty areas is a factor in the greater utilization of hospital and other institutional facilities by this population. The largest resource for both ambulatory and in-patient services for the poor population is Cook County Hospital. Indeed, it is the largest purveyor of medical care in the State of Illinois. It is the only "public" hospital in Cook County. Unlike New York City, which has 18 public hospitals, and which also purchases beds in private hospitals for the care of the indigent, there is only one "public" hospital here, and no beds are purchased in private hospitals for indigent patients by Cook County.

Last year there were approximately 65,000 admissions to Cook County Hospital, a reduction from earlier years.[6] Each day of operation, in the ambulatory Fantus Clinic, approximately 1,000 patients are seen.[7] This is exclusive of the number seen in the emergency and ad-

mitting area, which was approximately 1,200 every 24 hours a few years ago.[4]

The care in Cook County Hospital is alleged to be free. However, this "free" care hospital has a higher proportion of collections for its in-patient services than do most private hospitals. In a recent six-month period, 78 percent of the charges for hospital patients were collected from third party sources.

Other hospitals which serve this population generally are the teaching centers. The largest purveyors of care among these are Michael Reese, Mount Sinai, the University of Illinois, the University of Chicago, and Presbyterian-St. Luke's. Hospitals like Bethany Brethern and Garfield Community also have a high proportion of poor patients but the numbers are small and thus are not included. Others, such as Illinois Masonic, Wesley, Passavant, etc. also provide services on a smaller scale. Far and away, however, Cook County Hospital accounts for the medical care to the indigent and medically indigent. Patients from the non-poverty areas of Chicago distribute evenly across all the city's 95 or so hospitals with no more than three or four percent from any community area making use of any single hospital. But 23 percent of all cases from the 24 poverty areas were admitted to one hospital, Cook County. This may be lower than a hospital-discharge study done in 1965 when 29 percent of all cases from those areas went to Cook County.[8] However, results of the 1970 discharge study are open to question. If indeed the percentage is down, the passage of Titles 18 and 19, Medicare and Medicaid, which gave some choice to poor people as to their place of hospitalization is probably responsible. County Hospital's average daily bed census has dropped from 2,000 to 1,400 in the last 15 years. Cook County is also the primary hospital for the black population. Eighty-five percent of its beds are occupied by black patients. This one hospital accounts for half of all black Chicago patients.[5] With County's excellent record of collection from third party sources, the issue must be raised as to why these same patients could not be covered by those same sources in private hospitals. This situation persists despite the advent of Medicare and Medicaid. It persists despite the existence of the Office of Economic Opportunity and other neighborhood health centers administered by private hospitals; it persists despite the fact that more black physicians have staff appointments in private hospitals than previously. It will continue to persist until Cook County Hospital is eliminated, in its present form, as the dumping ground for the black and the poor, and the private hospitals can and will assume responsibility for care to this population. Then and only then will race, as well as finances, cease to be a determinant of access to health care. Cook County is the fulcrum of the dual care system and while it exists, the dual care system will exist.

The last of the three building blocks that must be mentioned is, of course, the first—money. There were 70 billion dollars expended for health care in the United States in 1970 by all sources. That figure comes to more than $300 for every man, woman and child. This is not cheap and one wonders if the population could not be cared for adequately at this level if there were a restructuring of the health care system and its financing mechanisms. In the city of Chicago, in 1968, there were 400 million dollars expended by all public sources, federal, state and local, for the care of the indigent, or about $400 per indigent person. It might be adequate if used appropriately. The inappropriate use of the medical-care dollar is, of course, a vast topic itself. However, I want to describe briefly the differences between the expenditure of the medical dollar for care to the poor and for care to the affluent. The medical welfare assistance programs are well known to be among the most expensive programs in Illinois. Even though about half of the dollars are from federal sources, Illinois must pay the other half.

In 1965, Lepper and Lashof carefully

examined medical welfare expenditures and found that only 12 percent of the medical dollar was paid for physician services, while 48 percent was paid for institutional services in the program covering recipients of Aid to the Families of Dependent Children (ADC). The affluent patient, or the one able to pay for his own care, spent 27 percent of his medical dollar for physician care and 30 percent for institutional services.[4] The Public Aid Department journal showed that between 1961 and 1967 the amount spent for physicians' services in all programs has continued to drop, while the amount spent for institutional services has continued to rise. In 1961 the proportion spent for physician care was 9.5 percent, in 1967 the proportion was 8.8 percent.[9] The last figures available for 1969 show that approximately 7.0 percent was spent for physician services in all programs.

There is something seriously wrong and uneconomic when a program pays premium rates for illness but provides little for prevention and detection. The current Illinois Medicaid statutes do not permit payment for complete physical examinations not connected with illness. They do not permit psychologic evaluation or other preventive services. The projected welfare cuts, if permitted, would create even greater problems for providers of health care and more suffering for the consumers. Being tested in the courts is the States' proposed reduction in public aid medical care services. If the courts rule that the reductions are permissible under the present laws, then, for Medicaid cash grant recipients, dental services would no longer be allowed except for pain, no podiatry services would be allowed, nor multi-vitamin tablets paid for. In the no-cash grant Medicaid group, known as MANG, physicians' visits would not be reimbursed, only clinic visits, and then only two visits each six months. There would be no out-patient x-ray, laboratory or drug services reimbursed. For General Assistance program recipients there would be no medical care permitted at all.

It is difficult to see the economy in these proposed measures when one notes that state researchers found, in a 1969 study, that the single most important reason why people were added to Aid to Dependent Children rolls in that year was a consequence of illness and resultant inability to work.[10] Sick people cannot work and therefore become dependent upon relatives or public sources. Reducing access to care can only, in the long run, contribute to greater dependency and more severe illness that must be treated in the hospital, where one finds the highest-cost portion of medical care. This will contribute to higher welfare costs as well as to greater suffering. Instead of further cutting medical assistance, the State would do well to concern itself with the human and economic impacts of the cuts and develop rational health planning for all the citizens of Illinois.

This discussion has been most cursory since I have tried to touch on a large number of topics, all of which deserve careful scrutiny. There has been no discussion of alternate or new models of health care that might address these problems. Other models of health care exist in foreign countries and in our own, and we should learn about them and from them. I do not know if it is possible to eliminate the dual care system or to develop a model system in the present times and climes, but we have no choice except to try if we are committed to decent, dignified, humane and adequate health care.

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5. DeVise P, et al: Slum Medicine: Chicago's Apartheid Health System. Community and Family Study Center, University of Chicago, Jan., 1969

6. Journal of the American Hospital Association: Guide Issue: Hospitals. Aug., 1971

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8. Hospital Planning Council for Metropolitan Chicago: Discharge Study. Feb., 1970; Feb., 1965

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10. Chicago Sun-Times: Illinois welfare study bares poor health care. Oct. 4, 1969, p. 36

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Bio-Mechanics

Rafelson ME Jr, Sky-Peck HH: On-line computerization of a clinical biochemistry laboratory. *Rev Informatique med 2 (1), 35-41, 1970*

A system for the on-line, real time computerization of a clinical biochemistry laboratory is described. The system employs small laboratory-dedicated computers and includes both hardware and software designed to perform all of the essential recording, test data collection, calibrations, clinical report generation, patients' file manipulations, and statistical analyses required by the laboratory. The authors describe the hardware and current operation programs.

Hematology

Booyse FM, Hohn DC, Rafelson ME: Studies on human platelets. VI. Study of platelet abnormalities by density gradient separation of platelet populations. *S.A. M.J. 43:964-967, Aug. 2, 1969*

Human platelets have been separated into four biochemically and morphologically characteristic populations (bands A, B, C, D) by density gradient centrifugation. Bands A and B contain platelet membranes and damaged platelets; bands C and D contain intact platelets with distinct internal structure. Quantitation of the platelets in each population gives a distribution curve which is virtually identical for normal individuals. The distribution curve is significantly altered in several conditions where platelet abnormalities have been described or suspected. Analysis of platelet distribution patterns provides a qualitative and quantitative method for studying normal platelets as well as clinical platelet abnormalities.

Immunology

Gewurz H, Snyderman R, Mergenhagen SE, Shin HS: Effects of endotoxic lipopolysaccharides on the complement system. *Microbial Toxins 5:127-149, 1971*

When endotoxic lipopolysaccharides (LPS) are incubated with fresh mammalian sera, a rich interaction ensues. Lesions indicative of the activation of the terminal complement components appear on the surface of the LPS, while, concomitantly, vigorous activation and consumption of the terminal complement components takes place. Activation of these components is known to promote phagocytosis, aggregation phenomena, the generation of anaphylatoxins, the production of factors chemotactic for neutrophiles, and membrane-damaging reactions. Indeed, endotoxins were found to cleave anaphylatoxins from the C3 and C5 components of complement and neutrophile chemotactic activity from the C5 component. Since it has long been known that injection of bacterial endotoxins into higher

vertebrates induces aggregation of platelets and neutrophiles, along with neutrophile accumulations, alteration of vascular permeability, and cytocidal reactions, it seems likely that certain of the biological effects induced by LPS are mediated via the complement system. In support of this hypothesis are the observations that endotoxins lose their ability to consume large amounts of terminal complement components after detoxification procedures which do not destroy their antigenicity, and that, *in vivo*, the early hypotensive phase of endotoxic shock in the dog can be prevented by prior depletion of terminal complement component activation.

The potential importance of the complement-LPS interaction is emphasized by observations that vertebrates, virtually throughout their ontogenetic and phylogenetic development, respond to endotoxic LPS by activation of complement components.

The pathway by which endotoxin induces terminal component consumption is not yet clear. Certainly, other serum factors are involved, because LPS has no direct effect upon the terminal complement components, but it is not yet known whether these include antibody and the earlier acting complement components C1, C4, and C2. The complement-LPS interaction can proceed in sera markedly deficient in immunoglobulin but at a diminished intensity. It is markedly impaired in human sera congenitally deficient in C1 and C2 and guinea pig serum depleted of C4 by a shark inactivator. Hence, these factors seem to be necessary to achieve the full intensity of complement consumption by LPS. However, it is possible, and likely, that additional serum factors (e.g. properdin) can be involved in LPS-complement interactions and/or that complement consuming enzymes additional to the C42 complex are formed on the LPS surface. Whatever the basis of the peculiar ability of LPS to activate the complement system, it seems that this pathway is utilized in the pathogenesis of acute glomerulonephritis and hypocomplementemic glomerulonephritis in man. An understanding of the basis for these contrasting profiles should reveal valuable insight into immunopathologenic mechanisms in these related diseases and into the means by which complement is activated by LPS.

Birdsey V, Lindorfer J, Gewurz H: Interaction of toxic venoms with the complement system. *Immunology 21:299-310, 1971*

Thirty-nine venoms from various vertebrate and invertebrate species were tested for their ability to consume haemolytic complement (C) activity upon incubation in fresh guinea-pig serum. Nineteen had "anti-complementary" activity, and these were provisionally sorted into the following groups: Pattern I—exemplified by the *Naja haje* (Egyption cobra) and six other Elapidae species (all cobras), which induced selective consumption of C3-C9, and led to formation of a stable C3-C9 consuming intermediate; Pattern II—exemplified by the *Bitis arietans* (puff adder), *Bothrops jararaca* (South American pit viper), *Agkistrodon rhodostoma* (Malayan pit viper), *Bothrops atrox* (Fer de Lance) and three other species, which induced marked consumption of C4 and C2, as well as C3-C9, but did not form a stable C3-C9 intermediate; and individual animals, e.g. the *Lachesis muta* (bushmaster), which induced other patterns (III-VI) of complement component consumption. Active fractions of representative venoms were partially purified by ion exchange and gel filtration chromatography and their interactions with the complement system characterized further. It is anticipated that these enzymes, with a capacity to activate the complement system in unique ways, will prove to be of further experimental usefulness.

Pickering RJ, Michael AF, Herdman RC, Good RA, Gewurz H: The complement system in chronic glomerulonephritis: Three newly associated aberrations. *J Pediat 78:30-43, 1971*

This report provides a description of three patients with chronic glomerulonephritis who present unique serum complement system deficiencies associated with different kidney histopathology and immunopathology. One patient has a severe deficiency of hemolytic Cl predominantly due to diminished Clr function; this abnormality is associated with the end stage of glomerulonephritis. A second patient has a selective deficiency of hemolytic C2

function associated with a membranous glomerulopathy. The third patient has hereditary angioedema with decreased levels of hemolytic C4 and C2; this patient's glomeruli show basement membrane thickening, centrolobular and glomerular hyalinization, mesangial proliferation, and interstitial round cell infiltration similar to that seen in patients with the C3-deficient form of chronic glomerulonephritis in children. The possible basis for the deficiencies and the questions that these natural experiments raise concerning the direct or indirect participation of the complement system in immune injury to the kidney are discussed.

Simmons RL, Moberg AW, Gewurz H, Soll R, Najarian JS: Immunosuppression by antihuman lymphocyte globulin: Correlation of human and animal assay systems with clinical results. *Trans Proc 3:745-748, March, 1971*

The immunosuppressive efficacy of an antiserum to human lymphoblasts was compared with an antithymocyte globulin and an antihuman lymph node globulin. Marked prolongation of skin allografts were noted. The prolongation was proportional to the dose of globulin. There were no significant differences noted between the three products except for the marked toxicity of the antithymocyte globulin. The prolongation is independent of the degree of histocompatability between donor and recipient as determined by tissue-typing techniques. The prolongation is inversely related to the titer of antihorse globulin in the recipient. Augmented immunosuppression can be obtained when the immunologic unresponsiveness to the horse globulin is present. The best presently available technique for predicting immunosuppression in man is the inhibition of the local graft-versus-host-reaction.

The skin graft rejection assay in man was used as a basis for determining the dose of ALG to be utilized. With increasing ALG doses a dramatic reduction in the incidence of early graft failure has been noted in recipients of cadaver renal allografts.

Mozes MF, Gewurz H, Gunnarson A, Moberg AW, Westberg NG, Jetzer T, Najarian JS: Xenograft rejection by dog and man: Isolated kidney perfusion with blood and plasma. *Trans Proc 3:531-533, March, 1971*

Renal xenograft rejection can be reproduced by isolated organ perfusion with heparinized heterologous blood. The pig kidney perfused with dog blood demonstrated (1) immediate decrease in renal blood flow; (2) antibody, C, WBC and platelet utilization; (3) deposition of IgG, β1C and fibran; which resulted in (4) vascular damage and interstitial hemorrhage.

Perfusion with cell-free heterologous plasma results in deposition of IgG and C with only a transient decrease in renal plasma flow. Perfusion with heterologous RBCs, WBCs and platelets in a plasma-free medium results in absence of rejection. Decomplementation of the perfusate by heat or EDTA prolongs organ survival with absence of the initial vasospasm. Partial removal of preformed antibody (with C intact) gives limited prolongation. Decomplementation plus removal of preformed antibody gives the best prolongation.

The results support the concept that the mechanisms involved in the rejection process are initiated by antibody-antigen complex, with activation of C, resulting in vasospasm and endothelial destruction. Platelet and WBC aggregation seems to be a secondary phenomenon. The participation of the clotting mechanism is not essential in rejection.

All xenogencic combinations studied resulted in prompt rejection except when sheep kidneys were perfused with human blood. This unexpected finding merits further investigation.

Gewurz H, Pickering RJ, Day NK, Good RA: Cobra venum factor-induced activation of the complement system: Developmental, experimental and clinical considerations. *Int Arch Allergy 40:47-58, 1971*

The cobra venom factor was found effectively to consume complement (C) in a wide variety

of species. An assay for the serum cofactor required for it to gain terminal C component-consuming activity was devised. Its concentration was much greater in guinea pig than in man. The cofactor was found to appear early in embryogenesis, to be present in a wide variety of species phylogenetically, and to be present in normal concentrations in the immune deficient bursectomized chicken and thymectomized mouse. It was present in normal concentration in sera taken from patients with a wide variety of human diseases, including agammaglobulinemia syndromes, certain other diseases known to be associated with repeated infections and malignancy, primary deficiency of C components and ongoing immune-mediated renal diseases associated with hypocomplementemia.

Therefore, this cofactor is widely distributed in nature, appears early in development, and its concentration is not affected by procedures known to greatly influence concentration of antibody and/or C components.

Nephrology

Mattenheimer H: Enzymes in the urine. *Mod Conc Ren Dis 55:1493-1508, 1971*

The pioneering developments in clinical enzymology during the past two decades permit the diagnostic application of enzyme measurements not only in blood plasma but also in tissue extracts and in preparations of subcellular structures. Up to this time, however, enzyme measurements in the urine have added little to the diagnosis and differential diagnosis of diseases of the kidney and the urinary tract. Early hopes that enzymes in urine may be sensitive and specific indicators for malignant tumors have not been fulfilled. Instead, the activities of several enzymes are often elevated in various renal and nonrenal diseases. Elevated activity levels in the urine of one or more enzymes can at best signal the warning—and this may be helpful in screening a larger population—that the patient might suffer from a kidney or urinary tract disease.

The diagnostic enzymology of plasma and organs would not be as advanced as it is now had we not learned to read changes of enzyme patterns rather than activity changes of single enzymes. This technique does not seem to be applicable to the urine, at least not with the enzymes which were studied in the past. Urine constitutes a very unfavorable environment for enzymes, and the many factors which influence the activities probably effect the various enzymes to different degrees.

Although some controversy still exists about the origin of enzymes in the urine, most investigators now agree that enzymes with molecular weights exceeding ~69,000 are derived mainly from renal tissue; blood plasma, erythrocytes, and leukocytes have been overestimated as potential enzyme sources.

Research on enzymes in the urine continues, and one or more enzymes may be found which could be useful to the physician for the early recognition and differential diagnosis of renal diseases.

Neurology

Rahn AC, Zuber B: The source of cerebellar evoked potentials synchronized with stretch of the extraocular muscle: *Exper Neuro 31:230-238, 1971*

The source of cerebellar evoked potentials synchronized with stretch of the extraocular muscle was investigated in the cat. Short latency "on" and "off" evoked responses were recorded from the surface of the vernian cortex (Larsell's Lobules Vb,c; Lobules VI and VII) and the brainstem. Evoked potentials of equal amplitude and latency were recorded from the cerebellar surface after the cerebellar peduncles had been completely severed. Thus, it is concluded that the cerebellar surface potentials correlated with extraocular muscle stretch does not originate in the cerebellum as previously thought by other investigators.

Oncology

Shastri S. Slayton RE, Wolter J, Perlia CP, Taylor SG III: Clinical study with Bleomycin. *Cancer, 28:1142-46, 1971*

Bleomycin is an antitumor antibiotic produced by *Streptomyces verticillus*. Seventy-five patients with various neoplasms were studied using this drug. Fourteen out of 20 patients with epidermoid carcinoma of the head and neck region, five out of fourteen cases of lymphoma including Hodgkin's disease, three out of six patients with testicular tumors, and one patient with lymphangiosarcoma of the arm showed evidence of objective regression. Common side effects encountered were hyperthermic reactions, gastrointestinal disturbances, hyperkeratosis and vesiculation of fingers, alopecia, and stomatitis. Pulmonary fibrosis is a rare but serious complication. One patient in this series died of this complication. There was no evidence of bone marrow, liver, or renal toxicity. Bleomycin promises to be a useful therapeutic agent and merits further study.

Slayton RE, Shnider BI, Elias E, Horton J, Perlia CP: New approach to the treatment of hypercalcemia: The effect of short-term treatment with mithramycin. *Clin Pharmacol Ther 12:833-837, 1971*

An intravenous bolus injection of mithramycin (25 μg per kilogram) was given to patients with malignancy-related hypercalcemia persisting after hydration. In most instances a gradual but steady fall in the serum calcium occurred within the next 48 hours, accompanied by a fall in serum inorganic phosphate and 24-hour urinary calcium excretion. Patients with head and neck cancer, cancer of the lung, and multiple myeloma were somewhat less responsive as a group than patients with cancer of the breast or kidney. Aside from transient nausea and vomiting, side effects were minimal. Small doses of mithramycin inhibit bone resorption; dactinomycin and other RNA inhibitors block the action of vitamin D *in vitro*. The hypocalcemia following administration of these agents may be an expression of their antivitamin D action.

Pathology

Eisenstein R, Sorgente N, Kuettner KE: Organization of extracellular matrix in epiphyseal growth plate. *Amer J Path 65:515-534, 1971*

Three cations of varying size and charge density, egg-white lysozyme, protamine and ruthenium red, were used to stain the extracellular matrix of epiphyseal cartilage growth plate. With these stains, it was possible to distinguish three types of proteoglycans or materials associated with them, which may well have as their major differences the type of cross linking to the tissue. One type was stained by ruthenium red and protamine but not by lysozyme, was extractable with 3 M guanidinium chloride and was relatively uniformly dispersed throughout the matrix of the growth plate. The other two types were stained by all three cations, were not extractable with 3 M guanidinium chloride and were intimately associated with fibrils. One of these was found on the collagen fibrils, was relatively scanty in the resting zone near the articular surface, relatively restricted to the extralacunar area in the columnar zones and appeared to diminish in amount in the hypertrophic zone. This material often had a 640-Å periodic array on the surface of collagen fibrils. The third type also was stained by all three cations and was not extractable with 3 M guanidinium chloride. It was distinguished from the other class of lysozyme-reactive matrix components by the larger volume of distribution occupied by the stained material. It also had a different distribution in that it was widely dispersed in the resting zone, was restricted to the lacuna

in the columnar zone and was absent in the hypertrophic zone. Thus, cartilage matrix as well as the chondrocytes undergo differentiation in the epiphyseal growth plate.

Eisenstein R, Scott RA, Lesak AE: Altered lipid and calcium binding by calcified aortic elastin. *Arch Path 92:301-305, 1971*

The lipid binding abilities of stretched and unstretched and of calcified and decalcified human medial aortic elastin were compared by immersing them in serum. Elastin bound more lipid if it were stretched than if it were not and more if it were decalcified than if it were not. These data and those of others suggest that arterial elastin is a molecular compartment in which calcium salts and lipids may be sequestered in finite amounts. If the compartment is filled with calcium salts, the capacity to sequester lipids is diminished and the lipids may gain access to arterial cells in larger amounts, thus inducing cellular injury. If correct, this hypothesis may provide a pathogenetic mechanism which could account for many observations which indicate that medial calcification promotes lipid accumulation in arterial walls.

Virology

Deinhardt F, Wolfe L, Junge U, Holmes AW: Viral hepatitis in non-human primates 1971 International Symposium on Viral Hepatitis. Special Issue, *C.M.A.J. 106:467 Feb. 26, 1972*

The attempts to transmit human infectious hepatitis (IH) to non-human primates are reviewed. Some species of marmosets are regularly susceptible to various strains of IH and the disease can be transmitted from marmoset to marmoset in series. Marmosets are resistant to second challenges with the same IH strains but are not necessarily resistant to other IH virus isolates. Some preliminary data on biophysical and biochemical characteristics of human IH viruses are presented.

A virus (K-30) allegedly isolated from an acute phase serum of a volunteer infected with the MS-1 strain of IH was identified as a rodent parvovirus; it is probably a laboratory contaminant.

Wolfe LG, Smith R, Deinhardt F: Simian sarcoma virus: Focus assay and susceptibility of human cells. *Fed Proc 31:619, Mar-Apr 1972*

Simian sarcoma virus type 1 (SSV-1), a C-type RNA virus isolated from a naturally-occurring fibrosarcoma in a woolly monkey, induced fibromas or well-differentiated fibrosarcomas in marmoset monkeys (J. Nat. Cancer Inst. 47:1115, 1971). The experimentally-induced tumors and cell cultures derived from the tumors contained C-type virus particles. Virus produced by the tumor cell cultures induced transformation of marmoset fetal lung cells (MFL), grown without agar overlay. Foci of piled up, spindle-shaped cells appeared as early as four days after infection, with little or no tendency toward satellite formation; final counts were made 21 days after infection. The titers of SSV-1 in unconcentrated supernatants collected from tumor cell cultures averaged 10^2 focus forming units/ml in untreated indicator cells but pretreatment of the indicator cells with 20 μg/ml of DEAE-Dextran for one hour before infection increased the titers at least 10-fold. Indicator cells inoculated with dilutions of SSV-1 beyond the endpoint of focus induction also produced C-type virus, and challenge experiments indicated the presence of a 10- to 100-fold excess of interfering, nontransforming virus. Human embryonic lung cells (WI-38), in parallel assays with MFL, were similarly susceptible to transformation by SSV-1.

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1. Gray GW, Bryan AC, Frayser R, Houston CS, Rennie IDB: Control of acute mountain sickness. Aerospace Med 42:81-84, 1971

List book references as follows:

2. Rafelson ME Jr, Binkley SB, Hayashi JA: Basic Biochemistry. Third Edition. New York, Macmillan Company, 1971, pp. 96-208

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Evan M. Barton, M.D.
Editor

QUANTITATION OF ANTICANCER AGENTS

Frederick A. Valeriote

The broad range of theoretical, diagnostic, and therapeutic applications of research in oncology has led the Section of Cancer Biology of the Division of Radiation Therapy, Mallinckrodt Institute of Radiology, Washington University School of Medicine, to combine a diverse group of researchers and clinicians in a broad onslaught on the problems of understanding and treating malignancies. Each member of the section has, in addition to a deep professional interest in at least one area of cancer research, a commitment to work closely with other scientists and clinicians, both within and outside of the section, and to aid in the training of research and medical oncologists at levels from undergraduate to post-doctoral. The areas of specific interest within the section are illustrated in Figure 1.

One of the major thrusts in all of this diverse activity is the development of quantitative techniques for the analysis of the effects of drugs and radiation on normal as well as malignant cell populations. Accurate quantitation is essential in predicting effective protocols in treatment, in testing such protocols *in vivo*, and in forecasting problems in therapy. In making quantitative measures of cell populations in tumor-bearing animals and humans, both before and after the course of treatment, some investigators have chosen as their parameter the rate of change of solid tumor volume or diameter, others have used survival time, and still others have employed end-point dilution assays. Each of these methods has significant limitations, some of which are listed in Table I.

Measurements of tumor volume include acellular areas, dead cells and supporting tissues such as stroma and blood, making any evaluation in terms of destruction of malignant cells quite difficult. Further, the rate and degree of tumor volume change depends on the rate of removal of dead cells as well as the rate of proliferation of surviving cells. These highly variable parameters can interact to yield invalid data. Finally, the range of the assay is limited to about one decade, and for necessary extrapolation of the results possibly a further 10 decades is likely unwarranted. The main advantage of this technique is the ease of performing the measurement with a minimum of perturbance to the host and the fact that the assay is carried out in the host receiving the treatment.

Survival time determinations find major usage in chemotherapy, where the survival time of treated tumor-bearing animals is interpreted in cellular terms. While any prolongation of survival time is interpreted as resulting from the killing of malignant cells, any inhibition of cell progression (resulting from any of a va-

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Presented as the Second Henry Regnery Oncology Lecture at Rush-Presbyterian-St. Luke's Medical Center, on May 23, 1972

Frederick A. Valeriote, Ph.D., Head, Section of Cancer Biology, Division of Radiation Therapy, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri; Assistant Professor of Radiology, Washington University School of Medicine

Optimization of Radiotherapy and Chemotherapy Schedules
Cellular and Biochemical Mode of Action of Anticancer Agents
Mathematical Modeling of Therapy Schedules
Kinetics of Normal and Tumor Cell Populations
Immunology of Normal and Tumor-Bearing Hosts

Fig. 1—Diagrammatic representation of our major research areas.

riety of agents) would also produce some degree of prolongation, even though the body burden of malignant cells might not be reduced by treatment. Further, survival time might depend strongly on drug disposition, since tumor cells can exist in locations which a given drug cannot enter. Last, there is a high degree of variability from animal to animal, and while many decades of cell survival are within the range of this assay, most investigators use it at a low sensitivity, the results usually being within a decade. The advantage of this assay is that it measures the effect within the host bearing the tumor.

The end-point dilution assay is an excellent cellular assay. Its main disadvantage is the necessity of preparing monodisperse cell suspensions. In the case of solid tumors especially, preparation of such suspensions by mechanical or enzymatic procedures can lead to a significant degree of cell killing. Also, a syngeneic tumor-recipient relationship must be maintained to minimize immune effects. These assays are known for their variability and for the large number of animals

TABLE I

QUANTITATION PROCEDURES

Tumor Volume	1. Assays acellular and necrotic areas 2. Assays stromal and other non-malignant cells 3. Depends on rate of removal of dead cells 4. Greatly underestimates the degree of malignant cell destruction 5. Limited assay range
Survival Time	1. Assays inhibition of cell progression as cell killing 2. Is complicated by drug disposition 3. Variable and low sensitivity
End-Point Dilution Assay	1. Transplantation artifacts 2. Requires large number of recipients

required per determination.

In searching for a better means of quantitation, the Cancer Biology Section has been working with the spleen colony assay. This assay has the drawbacks of all transplantation assays but is quite reproducible, sensitive, and has a range covering many decades. Its major advantage is that it quantitates the proliferative capacity of individual treated cells, yielding relevant and easily interpretable data. Quantitation of leukemic cells by spleen colony assay is illustrated in Figure 2.

Groups of mice are injected with 10^6 leukemic cells intravenously. Four days later (about 1.5 days before death) these mice are administered some treatment, be it a single injection of an anticancer agent or a more complicated schedule involving more than one agent (including x-radiation). Some time after the completion of therapy, usually 24 hours, the mice are killed and a monodisperse cell suspension is prepared from their femoral marrow (or spleens), a fraction of which is injected into each of the recipient mice. Eight days later, these recipient mice are killed, their spleens removed and placed in Bouin's fixative, and the number of macroscopic colonies counted. From the known fraction of the initial cell suspension injected, the number of "colony-forming units" per donor organ can be estimated. Each of these colonies is derived from a single cell which has sub-

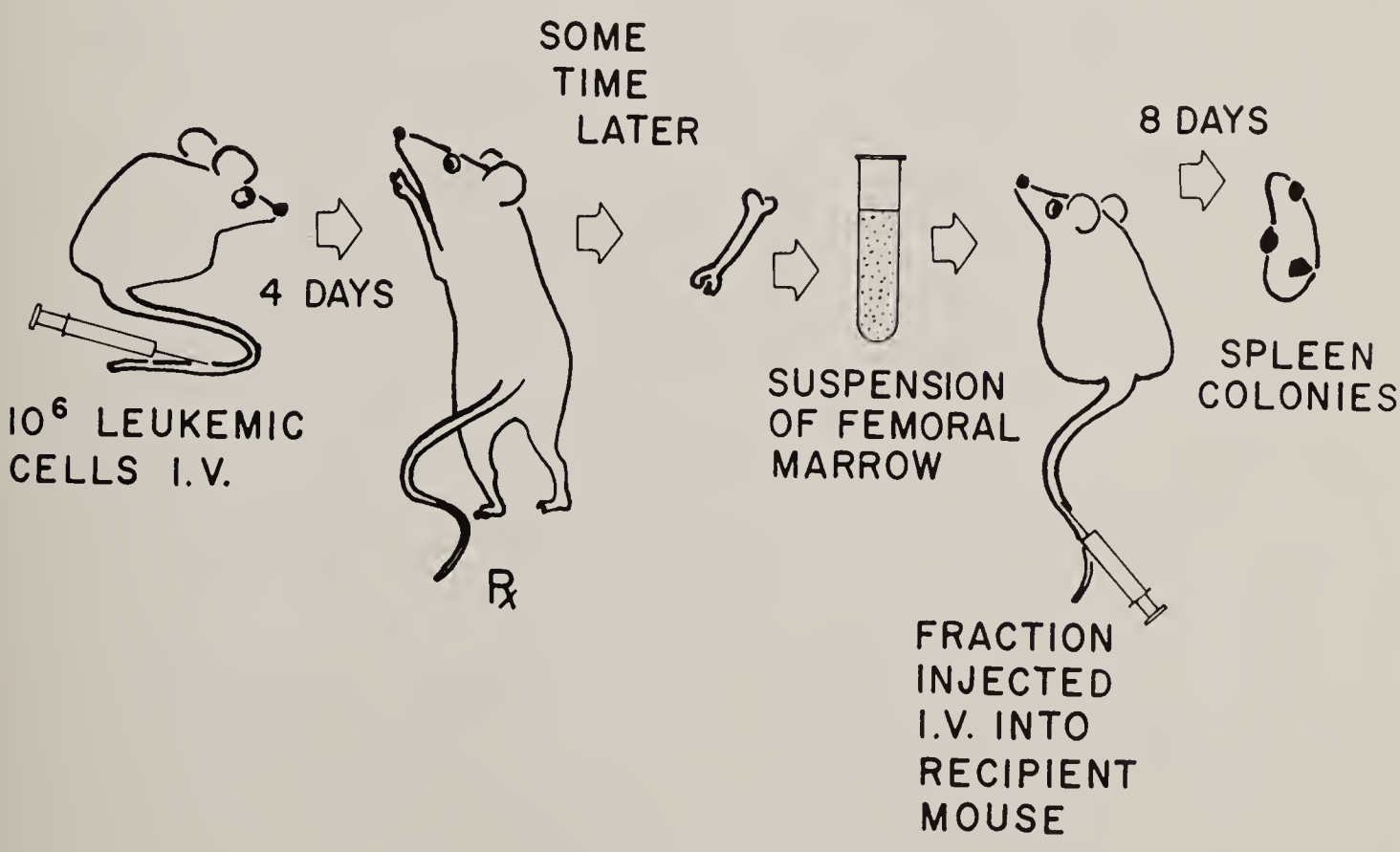

Fig. 2—Spleen colony assay for leukemic colony-forming units (LCFU).

sequently multiplied many times to form the colony. This determination is therefore a valid procedure for quantitating the number of malignant cells—that is, cells with unlimited proliferative capacity.

Using a similar assay, the effect of agents on the hematopoietic cell population can be determined. The assay of this normal cell population is relevant, since the limitation of chemotherapeutic aggressiveness is most often due to the destruction of hematopoietic (stem) cells. The assay is carried out as shown in Figure 3.

At some time following the treatment of normal mice with a given regimen, a monodisperse cell suspension is prepared from their femoral marrow and a fraction of this suspension injected into previously irradiated recipient mice. Nine or ten days later, the spleens are removed and fixed and the number of macroscopic colonies determined. An estimate of the number of colony-forming units in the donor femoral marrow is then made.

These two assays were initially applied to dose-survival curves for a variety of anticancer agents, most of which are in clinical use. It was found that the agents could be placed into one of three categories on the basis of the shapes of the dose-survival curves as shown in Figure 4.

Class 1 consists of agents such as nitrogen mustard and radiation in which the dose-survival curves are exponential in shape on a semi-logarithmic plot and show little difference between the normalized dose-survival curves; that is, for a given dose of an agent, a similar survival level is reached in both cell populations. These agents have been termed nonspecific.

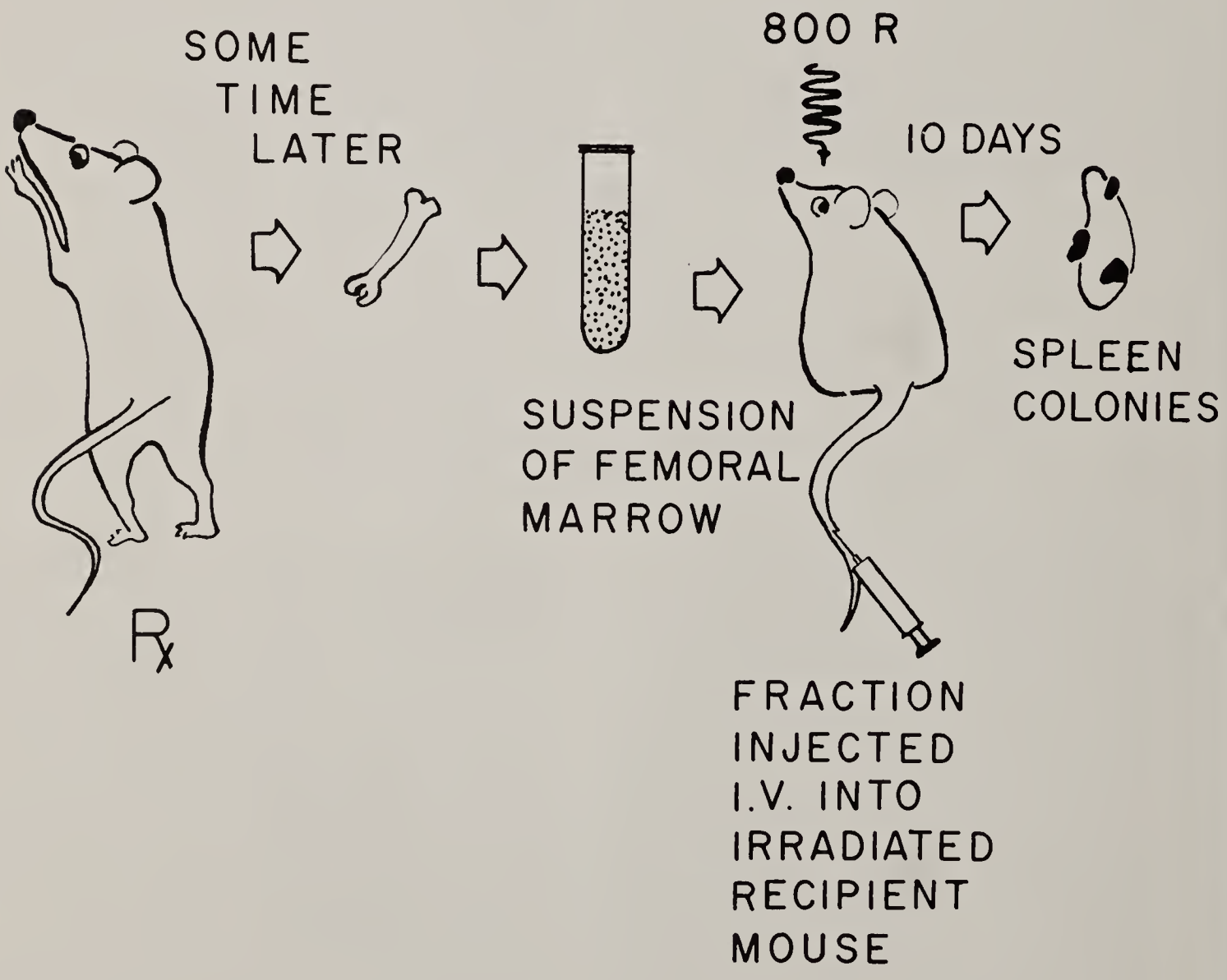

Fig. 3—Spleen colony assay for hematopoietic (normal) colony-forming units (NCFU).

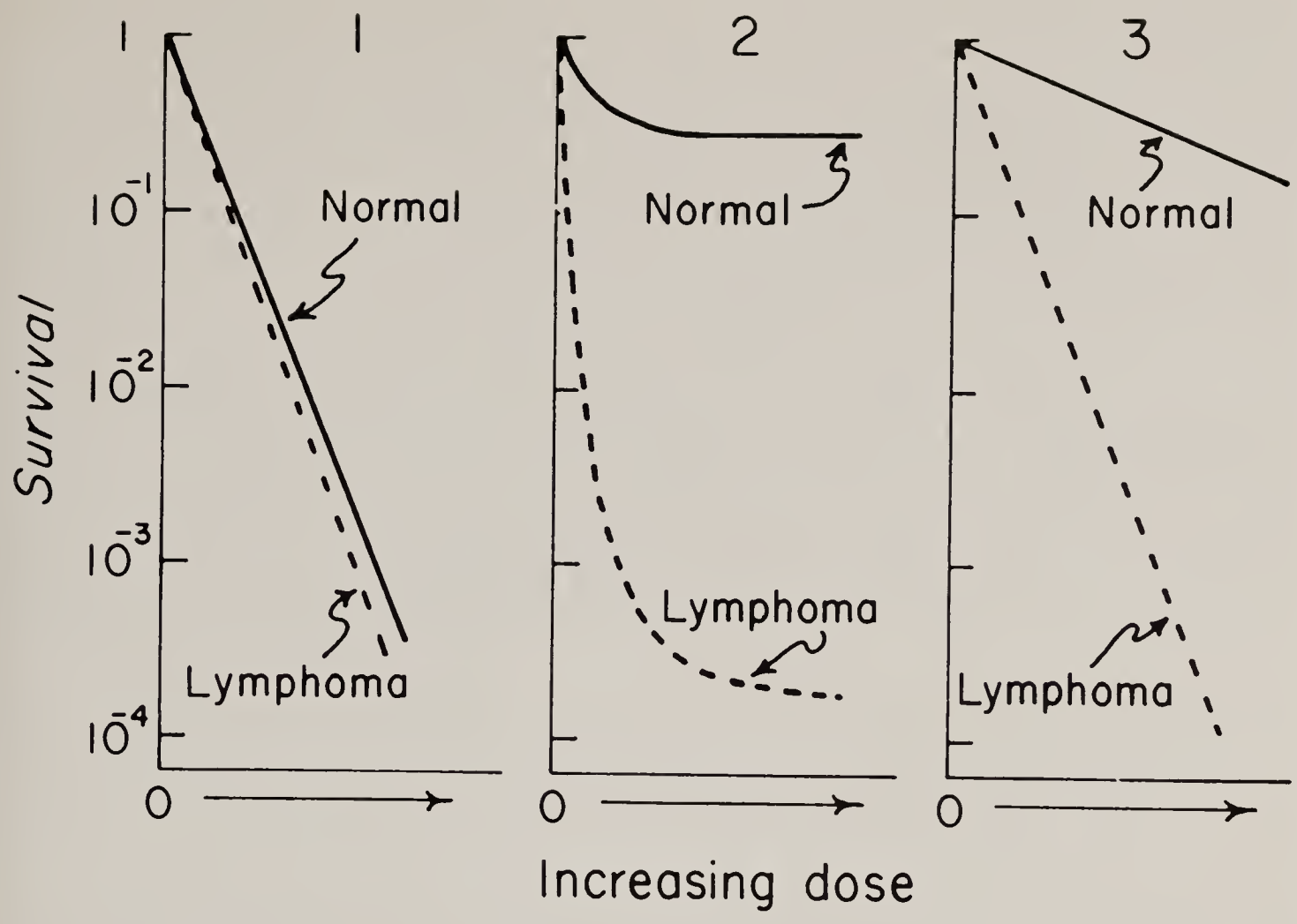

Fig. 4—Dose-survival curves for various anticancer agents.

Class 2 consists of antimetabolites such as methotrexate, cytosine arabinoside, and vincristine. There is a plateau in the dose-survival curve although some degree of selectivity in the killing of the two cell populations occurs.

Class 3 consists of agents such as cyclophosphamide, BCNU and 5-fluorouracil. As in Class 1 agents, the dose-survival curves are exponential in shape; but in this case there is a significant difference in sensitivity between normal and malignant cell populations. For example, a dose of cyclophosphamide which decreases the survival of the normal colony forming units (NCFU) to a level of 10^{-2} will decrease the leukemic colony forming units (LCFU) to a value of 10^{-31}.

Dr. Robert Bruce and the author proposed that the cellular basis for the differential action of these agents is a result of the difference in the proliferative state of the two cell populations, as illustrated in Figure 5.

Most of the normal hematopoietic colony-forming cells are not proliferating (at rest) while all of the leukemic cells are in cell cycle. As shown in Figure 6, agents in the first category kill nonspecifically—that is, whether the cells are in or out of

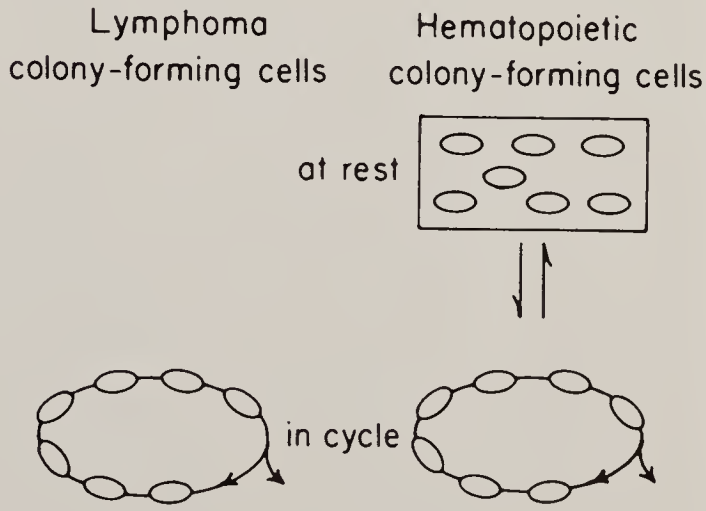

Fig. 5—Proliferative state of NCFU and LCFU.

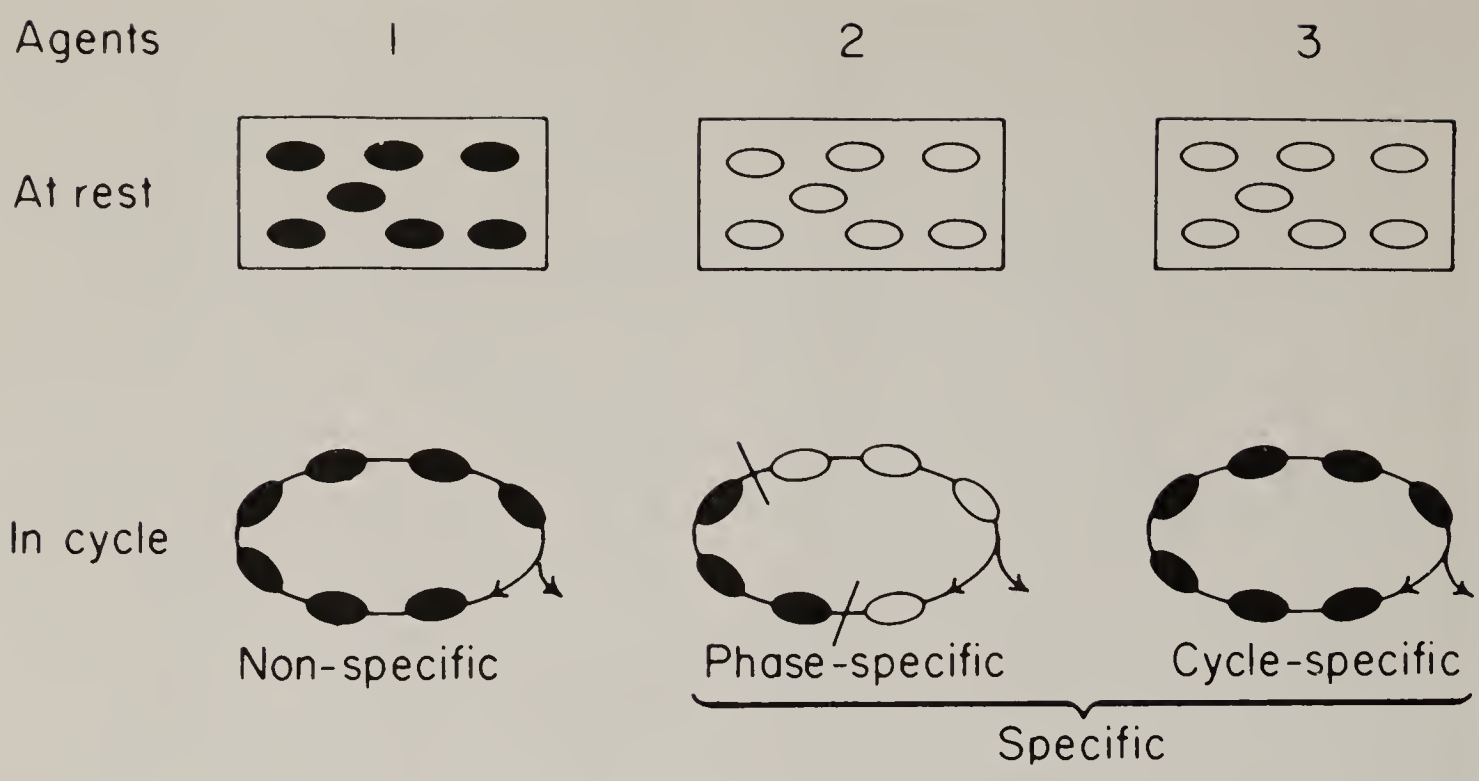

Fig. 6—Cellular interpretation of the action of different classes of anticancer agents.

cycle; those in the second category destroy cells only during some sensitive phase of the cell cycle, thus killing a fraction of the proliferating cells but not affecting the resting cells; agents in the third category preferentially destroy proliferating cells and will do so irrespective of the phase of the cell cycle that the cells occupy. There is a large amount of experimental data, both *in vivo* and *in vitro;* which supports this interpretation.

From these data and interpretations, one can make some predictions as to optimal approaches to the use of anticancer agents. Agents of the first and third categories can be given effectively as single large doses or as smaller, fractionated doses, while those of the second category should be given as multiple courses over a period of time corresponding to the generation time of the malignant cells. This latter point has been demonstrated recently by Dr. Skipper's group in their investigations of cytosine arabinoside. These predictions are simple and we can envisage conditions in which they may not apply strictly. For example, while it should make no difference how first-category agents are administered, it has been found that radiation is more effective for solid tumors when administered in a fractionated schedule. This is a consequence of the kinetics of recovery and repopulation of cell populations following treatment, as well as of their physiological states (such as degree of oxygenation) both before, during and after therapy. For Class 2 agents, it may be found that a single dose is as effective as multiple doses; this would follow, for instance, if the half-time for drug disappearance were fairly long. Also, while Class 3 agents should be effective whether given singly or multiply, we have evidence which indicates that although the normal cells are initially out of cycle, following a chemotherapeutic insult they do go into cell cycle, and in this state are as sensitive to anticancer agents as are the proliferating malignant cells; that is, the differential in sensitivity is lost.

Therefore, while cellular quantitation of anticancer agents allows the therapist to better understand and administer the agents, there are other factors which must be taken into consideration. One important factor is information concerning the types of cells which comprise the tumor and the interrelationships between them. A "typical" tumor, shown in

Figure 7, illustrates some of the different cell populations which must be considered before, during and after therapy.

Proliferating cells are the main point of therapeutic attack at present. Most anticancer agents can be administered so that they are effective in destroying a significant fraction of these cells. Non-proliferating G_0 cells are important since they are likely to be relatively insensitive to anticancer agents and are usually treated following their recruitment into cell cycle. Nutrient-deficient cells are of well-known importance in radiotherapy, where the nutrient is oxygen. It seems reasonable that chemotherapeutic agents

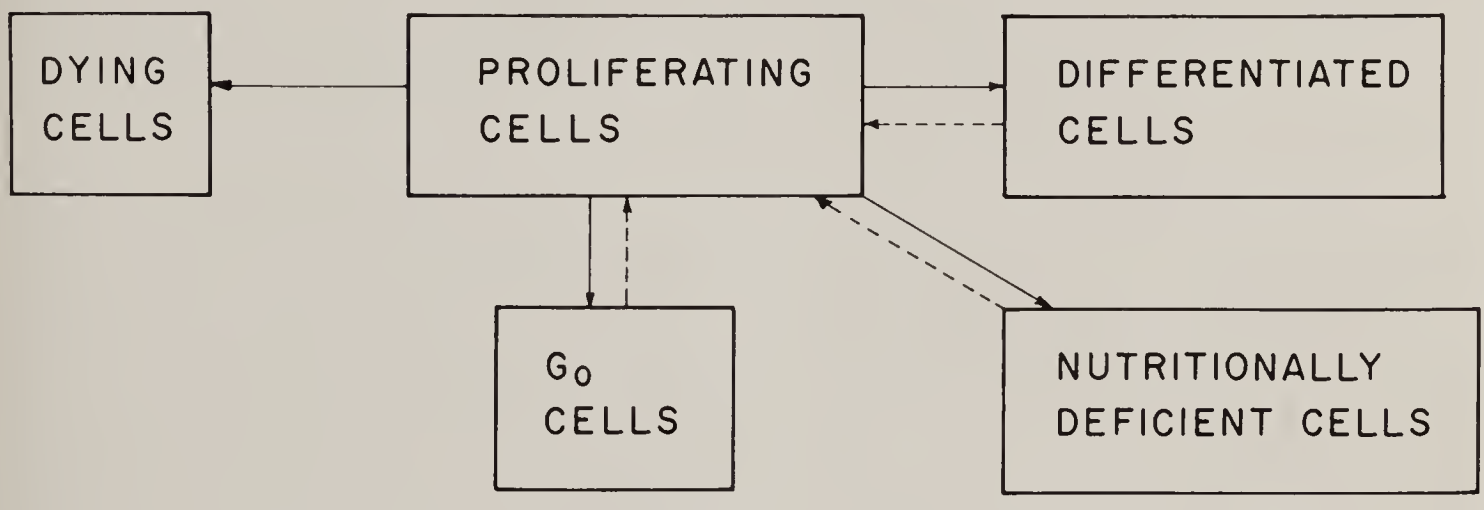

Fig. 7—The different cell compartments which might constitute a tumor.

would have difficulty reaching cells which nutrients have difficulty reaching and that such cells would appear as a drug-insensitive population. Immune response, rate and degree of metastasis, and other cellular factors are also important considerations. Thus, for a truly rational approach to tumor therapy, extensive information on the biochemical and cellular mode of action of the agents must be coupled with knowledge of the cell population kinetics of the tumor being treated. This information must then be refined further by consideration of the clinical limitations of the proposed therapy.

It is interesting that alkylating agents were found to occur in both non-specific and cycle-specific categories. To determine whether alkylating agents actually exist in two separate categories or whether a wide spectrum of differential activities occurs, the dose-survival curves for these two cell populations with a variety of alkylating agents were determined. The results for nitrogen mustard, thio-TEPA, NSC-82196, and cyclophosphamide are shown in Figure 8.

It can be seen that the agents have varying differential cell killing efficacies. To illustrate differential cells killing, a parameter termed the efficacy ratio, which is simply a ratio of the slopes of the dose-survival curves, was chosen. For nitrogen mustard this is obviously 1 and for cyclophosphamide it is 15.3. In Table II, a list of the ratios found for other alkylating agents is presented.

These results indicate that there is only one class of alkylating agents but that their effectiveness on different cell populations varies widely. Whether this same difference and ordering exists for other malignant cell populations is now being investigated.

One explanation for this difference is illustrated in a simple scheme shown diagramatically in Figure 9.

Different alkylating agents apparently have different efficiencies in their ability to diffuse intracellularly to the nucleus and alkylate DNA; some agents thus

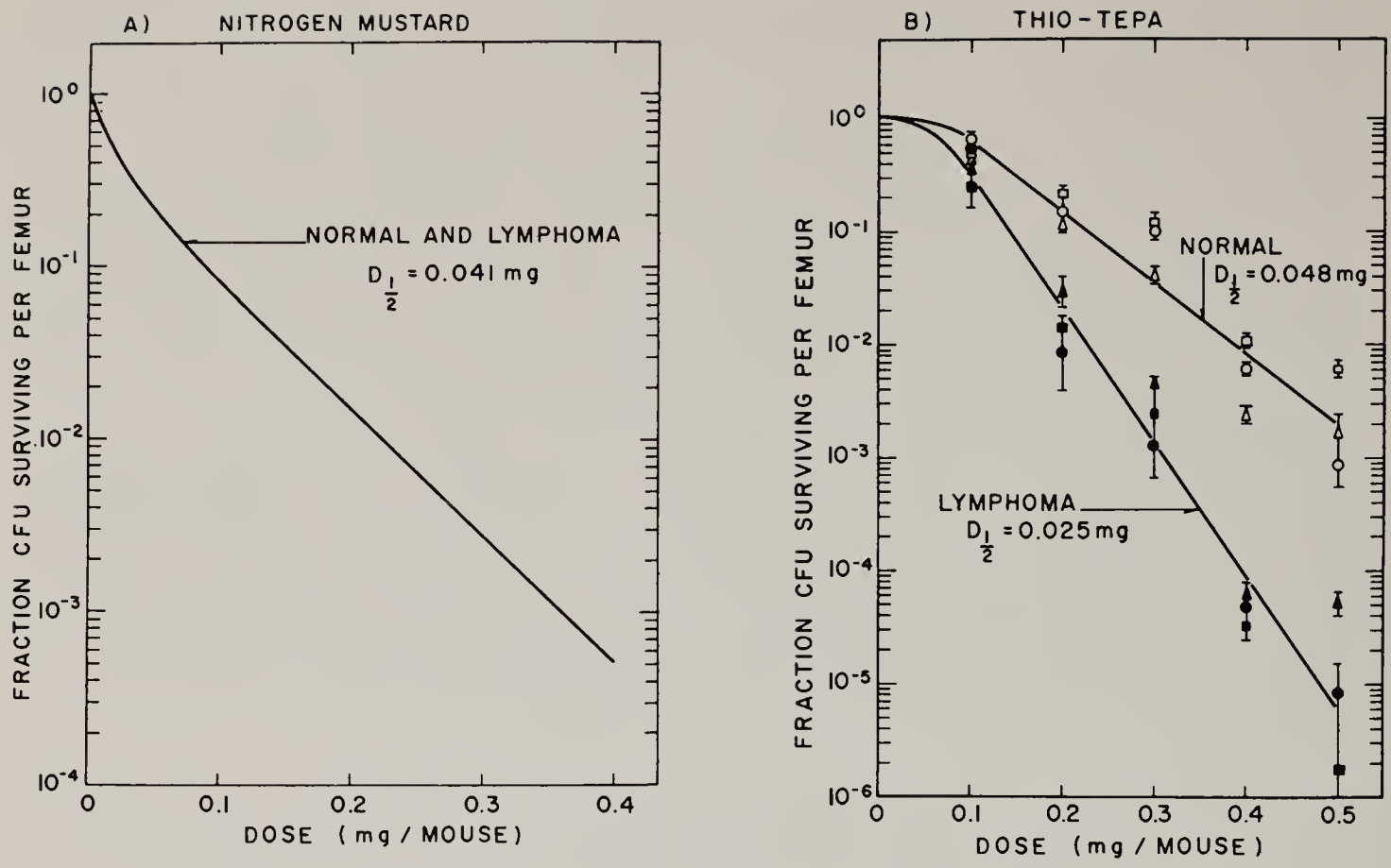

Fig. 8—Dose-survival curves for four different alkylating agents on NCFU and LCFU.

alkylate mainly cytoplasmic constituents while others alkylate a sizable fraction of nuclear macromolecules. However, the alkylation of DNA is probably much more effective in killing cells than alkylation of other molecules or macromolecules. Any agent which alkylated similar fractions of cytoplasmic and nuclear macromolecules in the two cell populations would presumably produce a similar

degree of cell killing and would thus be in the non-specific class. Nitrogen mustard would produce a "cytoplasmic" death as illustrated by the upper cell in Figure 9 and therefore be non-specific in its action.

TABLE II

ALKYLATING AGENT	EFFICIENCY RATIO
Nitrogen Mustard	1
Thio-TEPA	1.9
Phenylalanine Mustard	2.6
TEM	2.8
Chlorambucil	4.6
NSC-82196	8
BCNU	12.2
Cyclophosphamide	15.3

An agent such as cyclophosphamide, while apparently reaching the nucleus in both cell types as illustrated by the lower cell in Figure 9, has a less lethal effect upon the non-proliferating hematopoietic stem cell than on the proliferating leukemic cell. We believe this results from there being fewer "critical" sites in the resting cell available for alkylation, these being covered by protective nuclear proteins. This is not so in the proliferating cell, where "critical" DNA sites are operational and available for alkylation. Knowledge of the biochemical basis of this difference and of the mechanics of cell death will allow us to design and synthesize alkylating agents with higher efficacy ratios.

In any event, the most effective agents should be those with the highest efficacy ratios. Optimum curative schedules for their administration to tumor-bearing mice are being developed. Any agent which kills malignant cells will most certainly be curative if one uses the "correct" initial cell inoculum or period of time. For example, if we inject 10 malignant cells and wait say two days, it is most likely that whole body irradiation will cure these animals. However, interest in mice which showed "clinical" symptoms of cancer led to use of mice at four days after receiving 10^6 leukemic cells. There are about 10^8 malignant cells in these animals at the time of treatment. This implies that this tumor cell population must be decreased to a surviving fraction of less than 10^{-8} to obtain cured mice. A model for the curability of this tumor by single doses of anticancer agents has been built and tested on leukemia-bearing mice at one day and four days following cell injection. Figure 10 shows both the predicted and experimental curves.

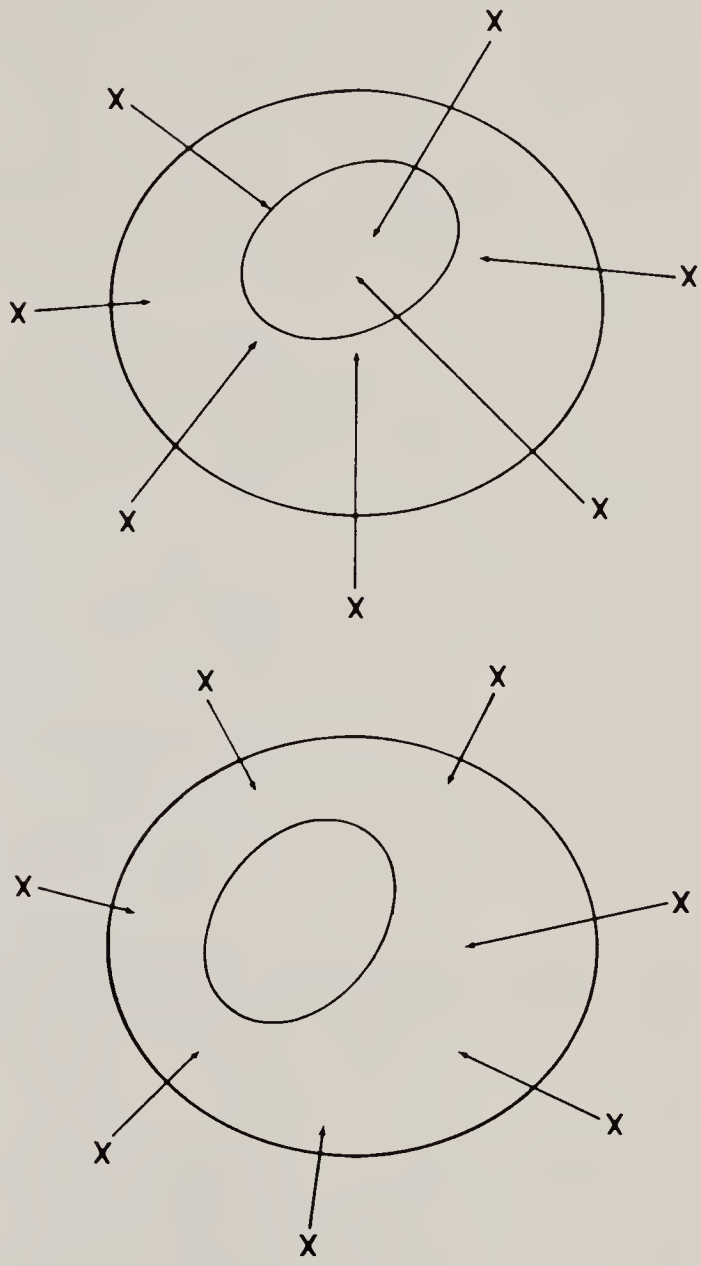

Fig. 9—Model for the action of different alkylating agents.

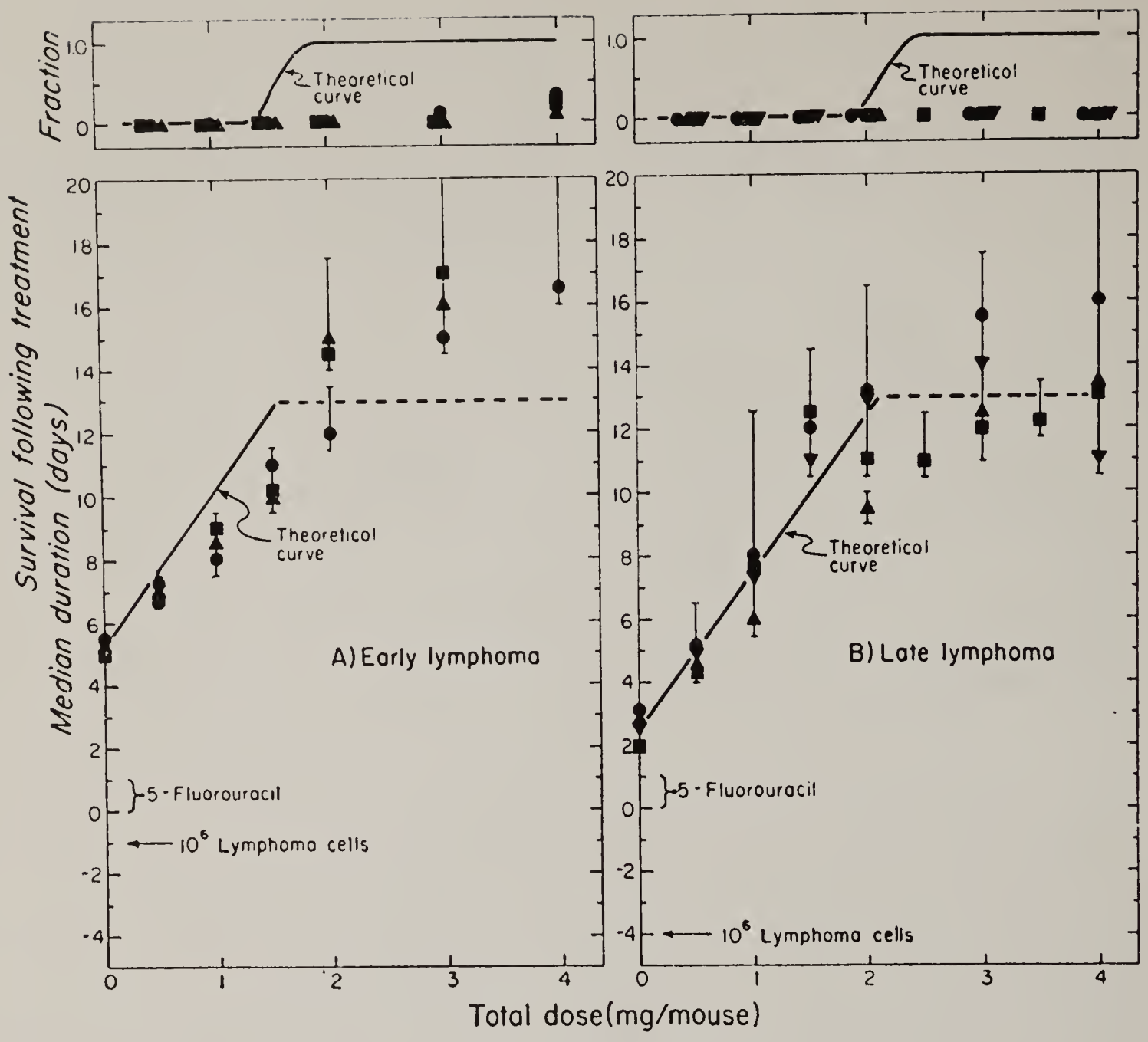

Fig. 10—Survival time and survival fraction of leukemia-bearing mice treated either one day (left) or four days (right) after receiving 10^6 leukemic cells.

We have plotted both the mean survival time and the fraction of mice surviving different single doses of this drug. The predicted results are shown as solid or dashed lines while the experimental data are shown simply as a symbol with an error term. It can be seen that while the survival-time data fit that predicted, the predicted surviving fraction is not attained. While some cures are obtained for the one-day tumor (upper portion of left figure), no cures are obtained for the four-day disease (upper portion of right figure).

It seemed that of all the parametric assumptions in the model, the one most likely to be at fault was the extrapolation of the dose-survival curve beyond the limit of sensitivity of the colony assay to values in the order of 10^{-8}. To test this, another cellular assay—an end point dilution assay—was employed. The assay is illustrated in Figure 11.

For this assay, a monodisperse cellular suspension is prepared from the tumor following treatment. In the illustration shown, a solid tumor is shown receiving x-radiation. In the present case, a spleen or liver, heavily infiltrated with leukemic cells, is obtained following cyclophosphamide administration. The cell suspension is then diluted serially and a fraction injected into each of a group of recipients. An end point, such as tumor develop-

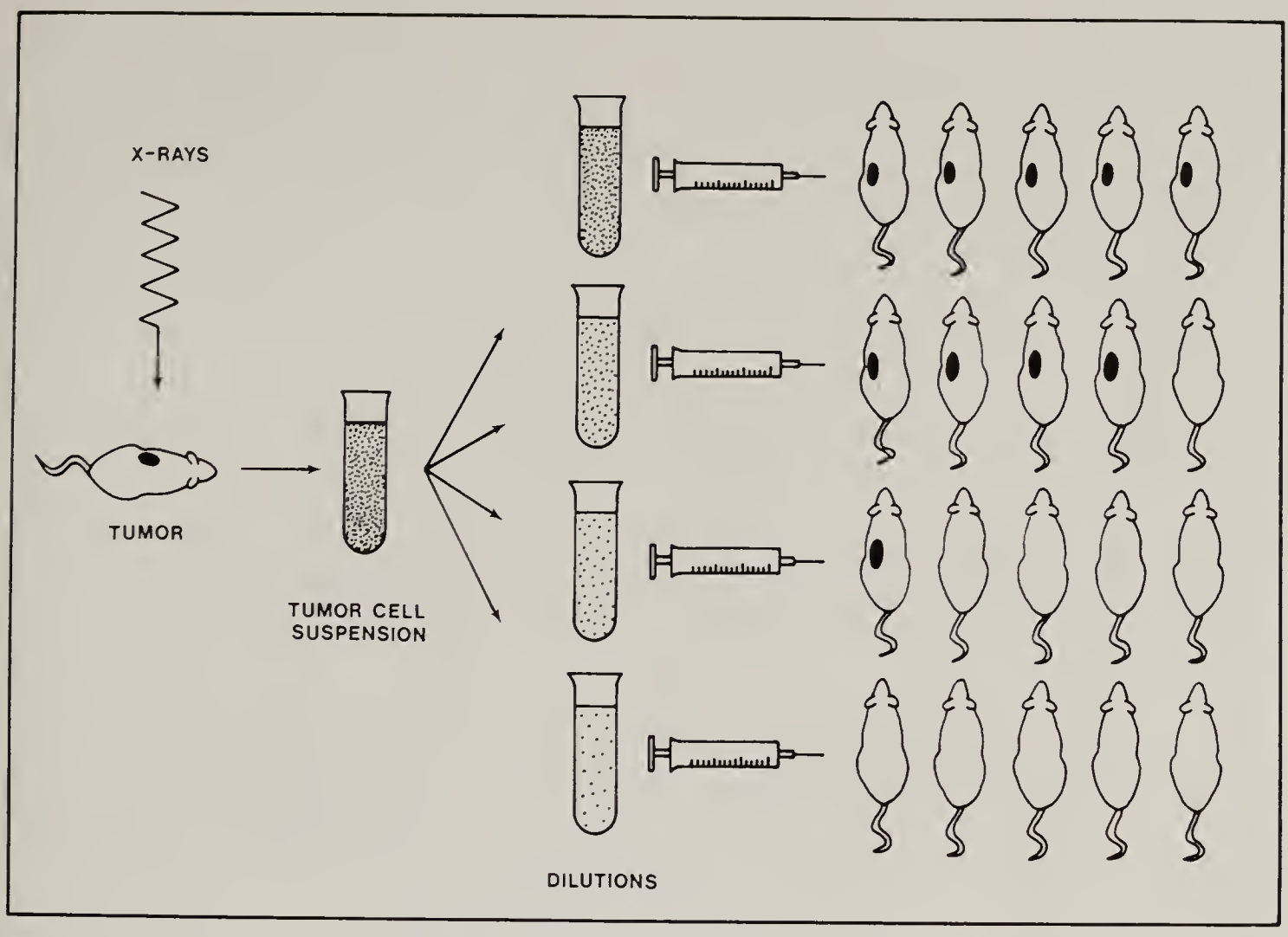

Fig. 11—Diagrammatic representation of the end point dilution assay.

ment or animal survival, is then determined after an appropriate interval of time. This value is then used to calculate the number of malignant cells in the initial tumor.

The survival of the malignant cell population in both the spleen and liver of leukemia-bearing mice was examined following the administration of cyclophosphamide and the results are shown in Figure 12.

It can be seen that the survival curve follows the expected value for about six decades of survival, after which there is a change in slope and even at the highest dose employed, malignant cells still exist in these organs. The existence of this resistant group of cells is the reason for failure to cure with this drug alone.

There are a number of possible solutions to this problem, such as employing fractionated doses of drug or giving other agents in combination with cyclophosphamide. Both courses are being investigated; some preliminary results of this research follow.

Initially, cyclophosphamide was combined with BCNU. The effect on the survival of leukemia-bearing mice was observed; the results of this study are shown in Table III where a dosage grid is constructed and the percent survival of the mice at 45 days is recorded.

An interesting "synergism" was found

TABLE III

		DOSE CYCLOPHOSPHAMIDE (MG/MOUSE)						
		0	1	2	3	4	5	6
Dose BCNU (mg/mouse)	0	0	0	0	0	3	0	0
	0.2	0	0	17	7	20	33	0
	0.4	0	0	33	33	73	73	40
	0.6	0	0	66	47	73	47	0
	0.8	0	23	80	60	60	83	10
	1.0	0	20	40	45	10	15	0

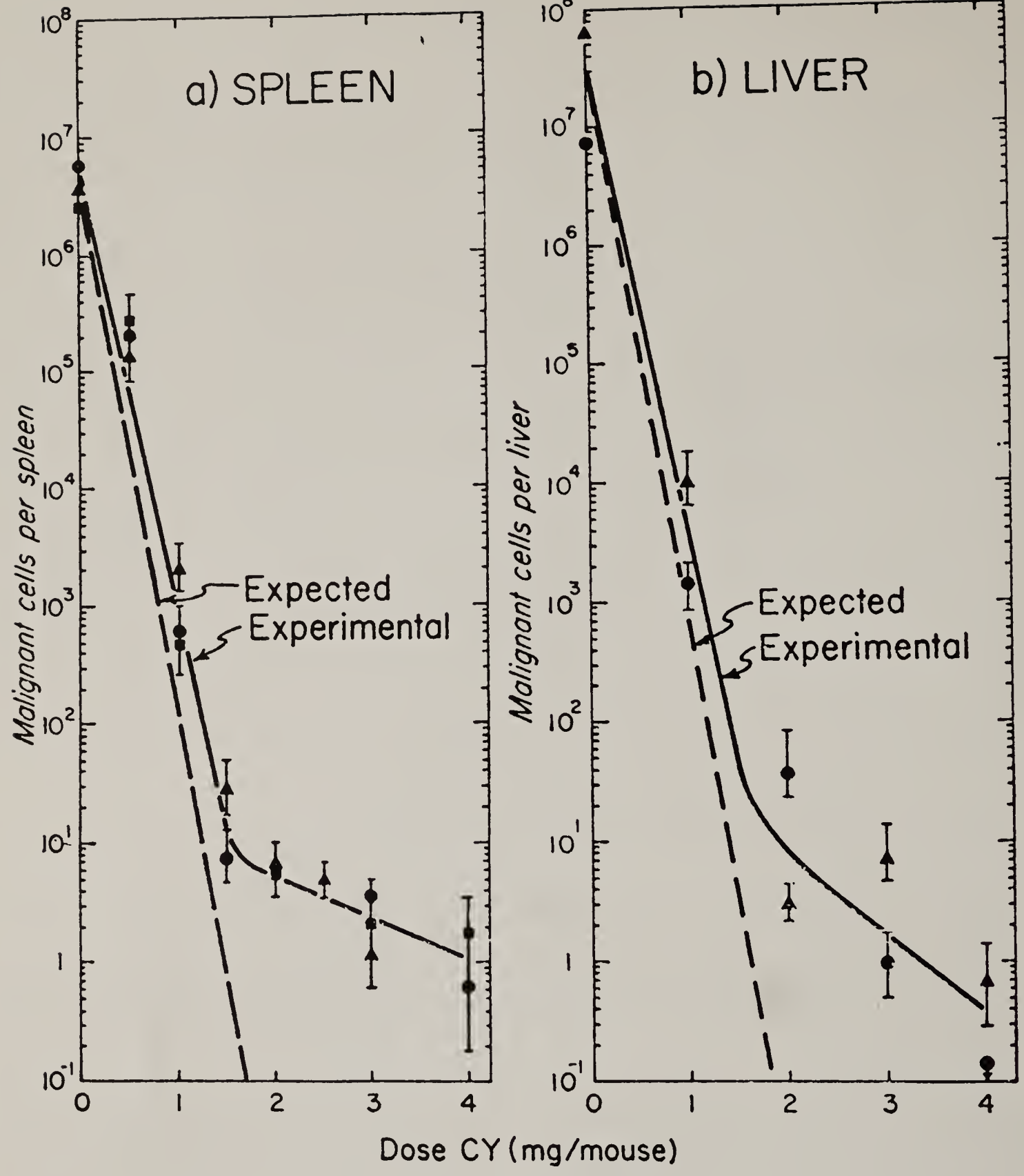

Fig. 12—Dose-survival curves of malignant cells in spleen (left) and liver (right) of leukemia-bearing mice following cyclophosphamide.

in that while neither agent by itself would cure animals with advanced leukemia, a number of combinations yielded a greater than 50 percent survival. It was also found that survival depended strongly upon the interval of time between the administration of the drugs. Subsequently, a major research program has been established under the direction of Dr. Teresa Vietti at the St. Louis Children's Hospital to examine the importance of time interval and sequence of administration to the effectiveness of anticancer agents used in combination.

The first combination examined was 5-fluorouracil and x-radiation. In carrying out these studies, information on the dose- and time-survival characteristics of

5-fluorouracil was required. Figure 13 shows the dose-survival curve for single doses of 5-fluorouracil; from this, a dose of 0.6 mg/mouse was chosen to study in combination with x-radiation.

From a similar study, we chose a dose of 400 R x-radiation. The time-survival curve for dose of 5-fluorouracil is shown in Figure 14.

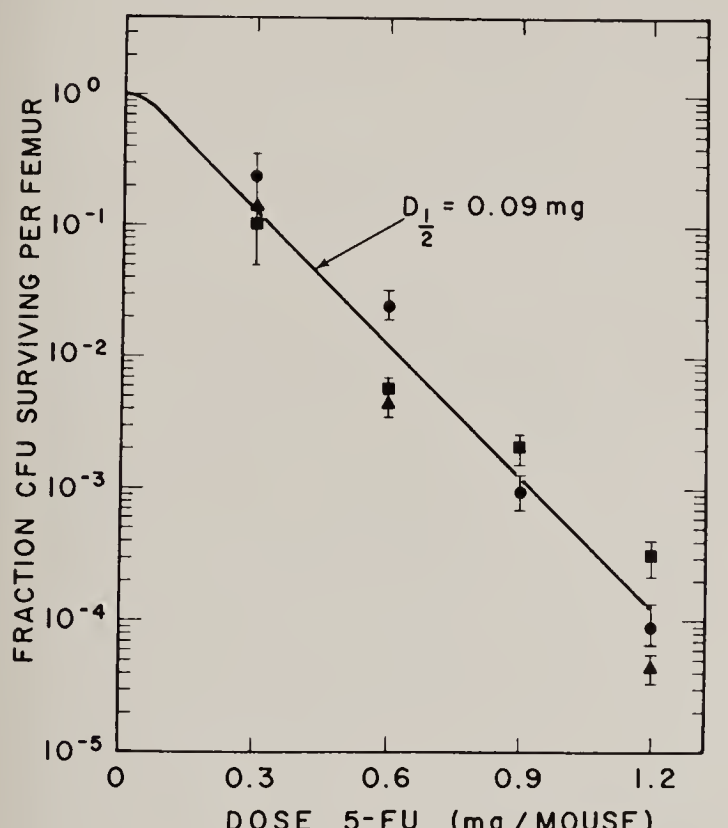

Fig. 13—Dose-survival curve for 5-fluorouracil (5-FU) on LCFU.

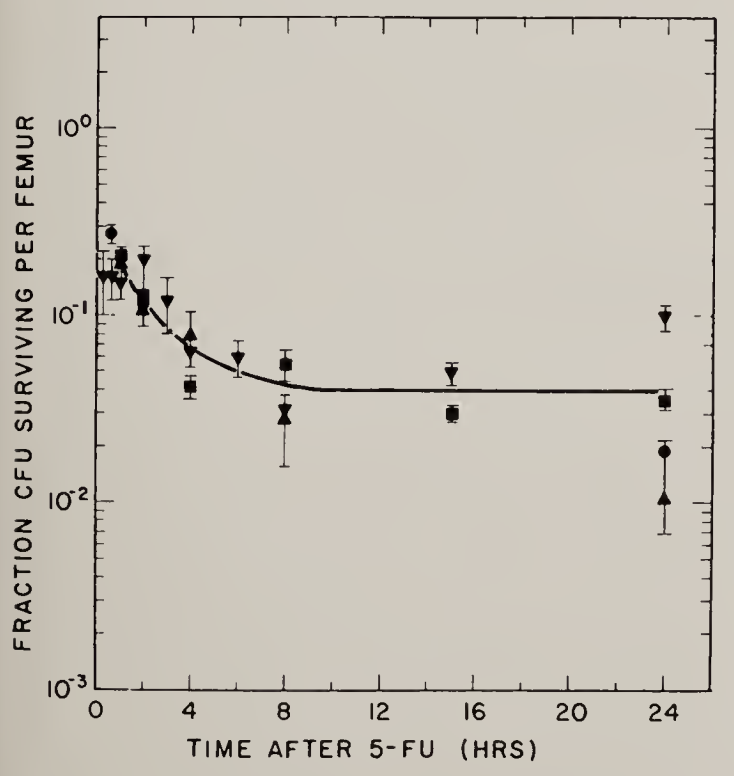

Fig. 14—Time-survival curve for 5-FU on LCFU

It can be seen that about eight hours are required following drug administration to effect maximum cell killing. This necessitates our waiting at least this period of time after administering the drug either alone or in combination before assaying the leukemic cells. When the two agents are given in combination and the sequence as well as interval between their administration varied, the results shown in Figure 15 are obtained for the survival of leukemic cells.

When the two agents are given together, an additive effect on cell killing is obtained. Similarly, when 5-fluorouracil is administered before the x-radiation, an additive or slightly synergistic effect

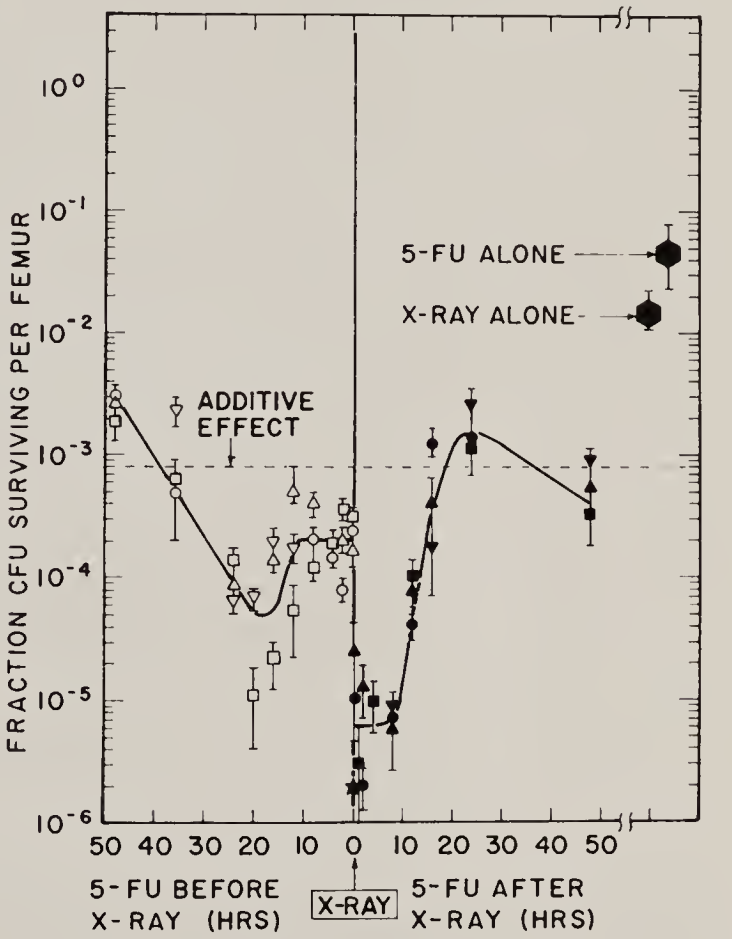

Fig. 15—Survival of LCFU following the administration of single doses of 5-FU or x-ray given either alone (hexagonal symbols at upper right) or in combination. Results for 5-FU given before x-ray are shown as open symbols and when 5-FU is given after x-ray, data represented by the closed symbols are obtained. The abscissa indicates the interval of time between the administration of the two agents. The dotted line indicating an additive effect is determined as the product of the survival resulting from the individual agents.

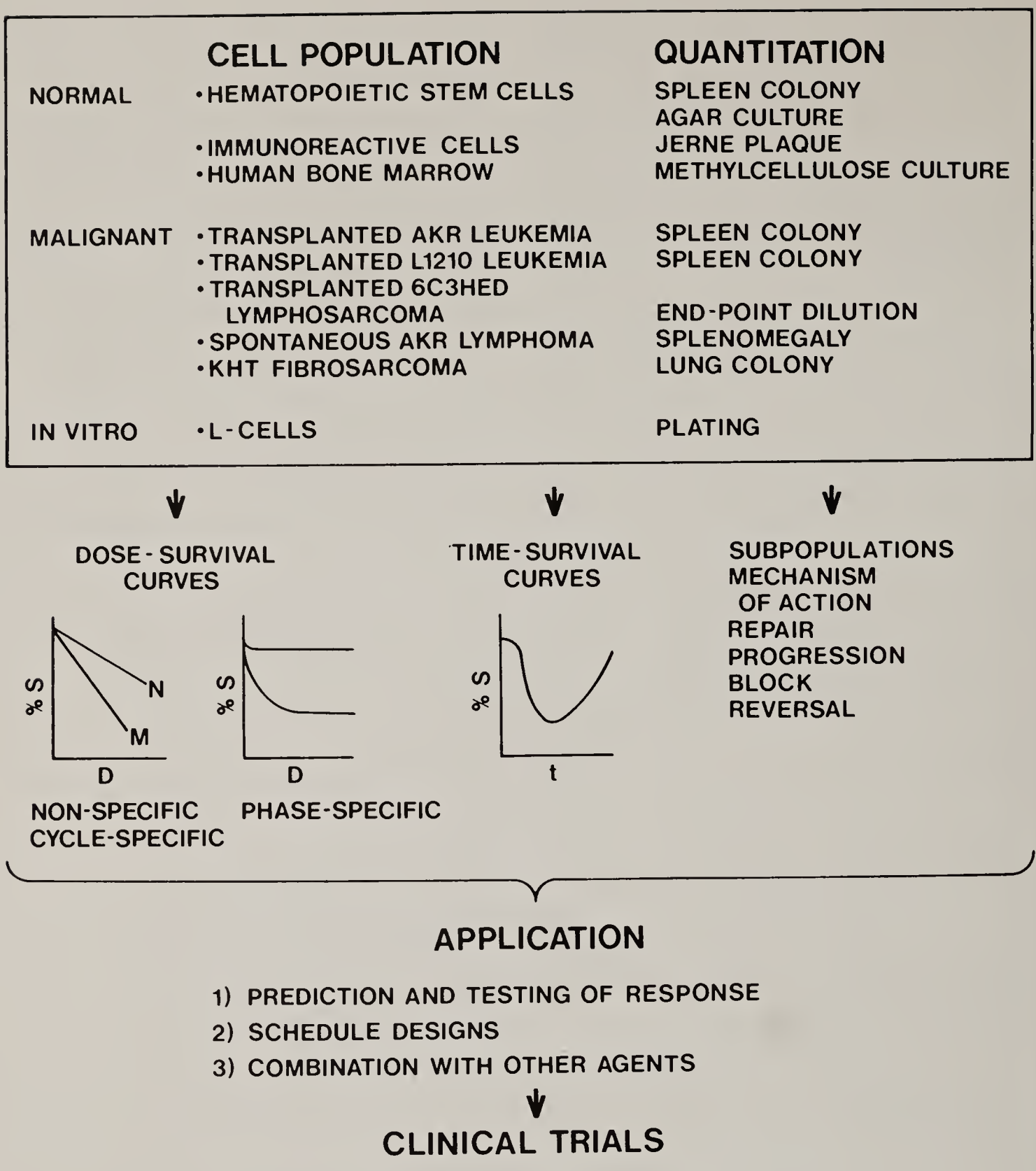

Fig. 16—Flow diagram of our approach to cancer chemotherapy.

is observed. However, when 5-fluorouracil is given within eight hours after the x-radiation, a significant degree of synergism occurs which is absent at later intervals. While the mechanism for this synergism is not known, it does not appear to occur in hematopoietic stem cells in mice. We believe that information such as this has applicablility in protocol design for human tumors in situations where these two agents are used together.

Figure 16 summarizes the approach and investigations which we are presently pursuing. We are quantitating the effects of agents on a wide variety of normal, malignant and *in vitro* cell systems as indicated in the top of this figure. The assay systems employed in this quantitation are also shown. Information on dose-survival and time-survival curves as well

as a number of other cellular effects are being studied for each agent. These data are then used either with the agent alone or in combination to design effective therapeutic regimens for experimental tumors. Finally, these results become part of the rationale in clinical trials on human tumors.

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THE PHYSICIAN, THE *SUICIDOCOCCUS CONTAGIOSA*, AND MEDICAL PRACTICE

H. L. P. Resnik

I have said elsewhere[1] that suicide prevention has been characterized by an historical lack of commitment by physicians, except when they are stimulated by social pressures, or perhaps when issues are phrased in traditional medical models. In this paper, I invite you to join me in a search for the amorphous *Suicidococcus contagiosa*.

Suicidococcus contagiosa

This pathogen is found dormant in the psyches of those who have lived with anyone who has killed himself. There are two species: The first, or more virulent is known as *S. contagiosa*, Type CS and has been isolated in the dormant state from the home of anyone who has killed himself. The organism, which is quite infectious, abounds where the deceased has had an especially close relationship with the patient. It may be transmitted by direct physical and emotional contact—such as by holding, kissing, or sharing personal experiences. The lethality rate is quite high where *S. contagiosa*, Type CS has killed a parent, sibling, or other important family member. The dormant state may be reactivated by loss of a loved one, strong unexpressed feelings of revenge, alienation, and loss of self-esteem. Symptoms that *S. contagiosa* is being actuated from the dormant state include a craving for alcohol or drugs, states of withdrawal and depression accompanied by fantasies of worthlessness or revenge, desires of reunion with loved ones, and pre-occupation with death and dying.

S. Contagiosa, Type SA, a less virulent strain, is found in psyches that have been exposed to those who have made a suicide attempt or gesture. The illness is characterized by an extremely high rate of reinfection. Patterns of transmission have not been fully determined and asymptomatic (possibly, physician) carrier states are suspected.

Physical properties: Both *Suicidococcus contagiosa*, Types CS and SA, are readily identifiable in the proper preparation. Take any patient suspected of having this infection; sit him down and take a "psyche sample" by the following technique: (1) Have the patient roll up his sleeve and bare his psyche; (2) Inject the following question directly into his psyche stream: "Have you thought of taking your life recently?"

Wait 30 seconds. Take the patient's response (or lack of it), stain with methyl blue, and examine under your clinical scrutinoscope. The organism also grows rapidly when cultured in an alcoholic medium. *S. Contagiosa*, Type SA is long and somewhat dagger-shaped with a distinct blue cast. *S. contagiosa*, Type CS differs in that the color has turned to gray—the most virulent forms have become black.

Presented before the Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, 3 February 1972

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The variety of suicidal behaviors is great. There are many more ways of ending one's life than by taking an overt, direct part in the act. For the moment, I will focus on overt and unchallenged suicidal behavior. The suicide rate has not increased appreciably in the past twenty years. The nearly 25,000 certified suicides in the United States, translates into a rate of approximately 11 per 100,000 population. There is no question but that this understates the numbers of actual suicides. The certification of an individual as a suicide is influenced by many factors and varies extensively in different communities. Until we have a more standardized method of evaluating and investigating suspected suicidal deaths, we can continue to view categories such as "accidental" or "undetermined" as statistical repositories for probable suicides.

Stengel[2] has shown conclusively that the suicide attempt (SA) group differs appreciably from completed suicides (CS). Another finding that a majority of suicides had made one or more prior attempts highlights the need for better predictive instruments for measuring lethality, or the CS probability. Suicidal activity ranging from a gesture through serious attempts has been *conservatively* estimated at a frequency of ten times for each suicide. (Current estimates range from twice to ten times that!) Such findings suggest that 250,000 people annually join a SA pool of those who are so unable to cope with their environment that they attempt temporary or permanent withdrawal from it. Simple arithmetic reveals that there presently exist in the United States approximately 2.5 million people who at one time in the last ten years have made a suicide attempt. In 1964, Mintz[3] reported a door-to-door public health survey in Los Angeles in which the prevalence of *Suicidococcus contagiosa*, Type SA was so high that he estimated the number of living Americans with suicidal histories as five million persons. Why have we been so unwilling to recognize the epidemic in our midst?

Who would care to address himself to that public health problem? Certainly, few professionals in preventive medicine have. Yet, any police or fire emergency rescue squad, any practicing physician, any emergency-room attendant, or hospital administrator will tell you that there is an alarming increase in the numbers of suicide attempters they see daily. How frequently are suicide attempters gavaged, sutured, or caffeinized, discharged, or held overnight, or most often returned to the very social and psychological circumstances that prompted the suicidal behavior! No systematic program for providing ongoing or follow-up care for the SA population currently exists in this country, although some communities are beginning efforts. I believe that ultimately we may need a judicial decision on the propriety of providing follow-up care for suicide attempters whose families may resist unsolicited professional intervention as an infringement of their civil rights. Yet, since both types of *Suicidococcus contagiosa* have been proven to be highly contagious, with exposure virtually guaranteeing infection, should not good public health practice demand that immediate follow-up with proper preventative measures be instituted? We do this for infections with the gonococcus, a much less lethal pathogen than the suicidococcus. However, to do this properly will necessitate an all-out public relations campaign. Herzog and I explored the problem of follow-up of survivors, and pointed out resistances ranging from denial of need to threats of legal suit and bodily harm.[4]

A manifestation of increasing citizen concern has been the burgeoning of suicide-prevention and crisis-intervention centers to the present number of 130. There are many models—rural and urban—operated both with and without professional consultation, and cooperative with, or independent of, the 24-hour emergency service of community mental health centers. I see these services as the initial phase of an evolving citizen commitment to bring its needy fellows more immediately to the resources which can assist them—a mental health ombudsman-type program.

However, there is a significant population at high-risk who may be infrequently served by a telephone-oriented, white, middle-class-operated group. Studies have shown that some seriously suicidal people will call, and be helped. Still, innovative techniques will be necessary to design services for the high-risk, infrequent callers: The aged (the socially isolated white male-over-60 syndrome, at a frequency nearly four times the national average), adolescents and college students (the second most frequent cause of death after accidents), American Indians (some tribes with suicide rates up to ten times the national average), urban slum dwellers (the incidence among the poor and among blacks is greater than previously recognized), and lastly, professionals—especially physicians—of whom approximately 100 (equal to a typical medical school graduating class) kill themselves annually. More active and efficient case finding techniques than are now available to us must be found; it is obvious that there is no one way to approach such a broad-based population. For instance, the high suicide rate among physicians, the finding that many physicians often see their patients anywhere from the very day (7 percent), week (23 percent) or 1 week to 30 days (27 percent or a month (50 percent) of the suicidal death,[3] and usually for somatic depressive equivalents,[5] the fact that patients often utilize the physician's own prescriptions to die, and the paucity of medical school curriculum time devoted to the acute and long-term management of suicidal patients—all suggest that a first step should be to sensitize medical students and other health professionals to suicidology.

The physician has been implicated increasingly as a psychopathogenic carrier of the *Suicidococcus contagiosa*. Schmidt, et al., found that 57 percent of the patients who suicided were having medical treatment at the time. The Motto and Green study[6] indicating that one of every two persons who had attempted or completed their suicides had seen a physician within the month, suggests that the physician may have had an opportunity to identify his patient's suicidal inclinations prior to the act. Personally, I know of few more disturbing losses to the physician than the suicide of the patient. Many physicians have discussed such cases at length with me, and I believe have been too fast to conclude that they could not have participated in preventing it. I believe errors of both omission and commission occur. Omitting to question a depressed person for suicidal intent is *not* a service. You do not activate latent ideas. Patients will welcome your question as an indicator of your tolerance to discuss the matter with them. An error of commission, as I view it, is to prescribe barbiturates for a depressed patient without considering carefully the likelihood of an imminent overdosage.

How does the physician act as a psychopathogen? One of the ways is by forgetting that his relationship with the patient is a most potent and therapeutic asset, no matter what the illness. The physician then becomes more vulnerable to abusing that relationship; at such times, he is most often unaware (unconscious) of it. Suicidal patients require protracted, unlimited and dependent relationships which can weigh heavily upon the time and energies of a busy practitioner. It is at such times that the tendency to over-prescribe oneself as a therapeutic agent may become psychopathogenic. When improvement does not occur and the patient continues with unchanged symptomotology, but with increased demands, the physician's response may range from irritation to anger to rejection. Such reactions can be manifest consciously, or, even more dangerously can be acted outside of awareness, i.e., by over-prescribing or permissively prescribing, or refusal to treat.

Gardner, Bahn, and Mack indicated 20 of 54 suicides of patients[7] with previously established psychiatric diagnoses occurred while they were still in psychiatric treatment, and a further 26 killed themselves within three months after their last psychiatric contact. Such statistics should dismiss the physician's hope

that referral of the suicidal patient to a psychiatrist will automatically result in marked diminution of the suicidal risk.

Litman[8] has pointed out the difficulty that trained psychotherapists encounter when dealing with suicidal patients. How much more taxing is the encounter of the physician who has had insufficient psychiatric training and experience to explore the intricacies of the doctor-patient relationship! For the person who is truly suicidal, only hospitalization and immediate electroconvulsive therapy have been shown to be efficacious. My inescapable conclusion is that, despite specialist training, knowledge and experience, it is often true that psychiatrists tend to underestimate or to overlook suicidal risk. However, by virtue of their experience, they are still in the best position to manage these problems directly or in consultation.

Formerly, the psychodynamics of suicidal behavior were viewed in a rather simplistic manner based on Freud's original formulations. That is, the angry, hostile wishes of an individual directed at another cannot be acted out for one reason or another and become retroflexed and directed at the internalized psychic representations of loved ones, both past and present, within oneself. This raises the question of the significant other whose threatened, anticipated or real loss often stresses an individual so that he will kill himself. Hendin, who studied the fantasies of suicidal patients, found that they equated death with seven general meanings (dependent on the particular dynamics of each case): retroflexed murder, reunion with a loved one, omnipotent mastery, complete abandonment, rebirth, atonement, and a conviction that oneself is already dead. He emphasized that when the fantasy of death offers a means of gratification, then suicide may be imminent.

A loss-stress of a loved one can be readily understood in the context of an interpersonal relationship. But it also must be understood in the terms of loss of supportive bodily functions (such as the inability to do things physically that once were possible) and loss-stress involving socially derived factors such as prestige and status.

Some of the signs the clinician should be trained to seek are the following: early morning awakening; any depression in which signs of agitation are present; a recent loss with significant depression—the loss may be of a meaningful person, of status, prestige, or of bodily parts; suicidal rumination in an individual who has made a prior suicide attempt; the added presence of psychosis or a history of previous psychosis, especially manic-depressive illness; an affirmative response to the question, "Are you feeling so badly that you are considering suicide?" The incidence is exceptionally higher when the patient has thought through a clear-cut plan. The risk is great when the patient is a male in his late forties; it greatly increases into the sixties at which time any talk of suicidal behavior demands immediate attention and probably hospitalization. Lastly a very clear change occurs in the ordered way of living of an individual who communicates to others important to him his plans to complete a will, distribute his effects, or indicates that they will miss him soon. Any combination of these will often be present.

There have also been a number of studies demonstrating highly significant correlations between the death of a parent in childhood or adolescence, and the attempt or commission of suicide by the surviving child in later life. This becomes even more significant when the loss of the parent was itself by suicide and challenges us with the very important public health and preventive medicine task of reaching the survivors (especially surviving children) of completed suicides. This is a problem of dealing with massive resistance, as Dr. Herzog and I have already reported.[4]

There are many self-destructive behaviors by which man may contribute significantly to his premature death. Some examples are: excessive risk-taking (e.g., crossing the street improperly; high-speed, reckless automobile driving; vol-

unteering for submariner duty); indiscriminate experimentation with "hard" drugs; victim-precipitated homicides (Wolfgang[9] describes a not infrequent situation where the victim of a lethal assault contributes directly to his own demise, that is, he gets someone else to take his life), and repetitive accidents, both industrial and personal. Specific self-destructive behaviors that should alert the physician, range from the diabetic's refusal to take his insulin as prescribed, although he has been clearly informed of his risk of losing parts of his body, to the post-coronary businessman who continues at the same or heightened frenetic pace, to the alcoholic with cirrhosis and varices, who continues to drink. Blachly[10] and Lunde[11] have independently reported that certain individuals, some wishing to serve as heart donors and others seeking heart transplants may be strongly suicidal.

For physicians who would rely upon the definitive diagnostic test to detect the *suicidococcus* in such patients, the urinary test reported by Bunney and Fawcett is quite preliminary[12]. The hypothesis was that high urinary 17-hydroxycorticosteroids, utilized as an index of psychologic distress, can be correlated with increased suicidal risk. They suggest that increased urinary levels of 17-OHCS reflect turmoil which clinically manifests itself as an increased index of suicidal potential. This hypothesis was originally suggested to them upon reading Spillane's 1951 review of nervous and mental disorders associated with Cushing's syndrome. Hansen and Levy could not confirm this.[13].

I am not sure that a hard anti-suicide line can be maintained under all circumstances. For instance, it is conceivable to me that as our aged population increases, as medical care for those near or *in extremis* borders on the heroic and sometimes unreasonable, self-determined suicide in harmony with medical, legal and pastoral consultation might become available to those who prefer to die a less protracted and more dignified death.

Individuals attempting suicide may have different preceptions of reality, time and space, death and dying, than do non-suicidal people. Anyone who has manned a suicide prevention telephone service knows that he can scarcely escape discussing with callers the various meanings of death. How many medical, nursing or public health professional schools even teach the fund of increasing information subsumed under Shneidman's neologism —"suicidology!" Health educators have been slow to deal with a variety of taboo topics, mourning, grief, death and dying being those most related to suicide. How many schools have such formal coursework? If students are fortunate, they may be exposed to a sensitive open clinician willing to share his feelings and his art of the practice of medicine, as well as his science. Such students may learn something about the terminal patient and his family, and the role of the physician in tolerating grief and facilitating mourning. Just as facing the dying patient brings the physician to the mirror of his own mortality, so, too, does the query to one's depressed patients, "Have you thought of taking your life?" bring the physician face to face with the self-destructiveness in all of us. One can hardly do this consistently and with commitment without training, experience, and the opportunity to share the burdens involved, with colleagues and family.

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THE NON-HODGKIN LYMPHOMAS—AN ASSESSMENT

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The therapeutic nihilism which prevails in the treatment of the non-Hodgkin lymphomas can no longer be excused or tolerated. This attitude derives from reports in the literature of the 1940's and 1950's (Table I). In 1947, Craver[1] reported three hundred patients and claimed only 25 percent five-year survival. Similar figures are reported by others.[2-7] As late as 1959, Cook et al.[8] could only report a 25 percent five-year survival for early stage lymphomas.

In contrast, Peters[9] was able to achieve 50 percent five-year survival in Stage I disease. Scheer[10] found a 60 percent survival free of disease in Stage I reticulum cell sarcoma and a 75 percent five-year survival free of disease in Stage I lymphosarcoma. This rather striking improvement was highlighted in 1971 by the report of Lipton and Lee[11] who found an 85 percent four-year survival free of disease for Stage I lymphosarcoma and reticulum cell sarcoma. Even though these successes have been overshadowed by the marked improvement in the control of localized Hodgkin's disease, such results do not permit anything less than a vigorous approach to proper staging and treatment in the non-Hodgkin lymphomas.

In this report, we present an assessment of the results of treatment of the non-Hodgkin lymphomas between the years 1960 and 1970. All patients with localized (Stage I) or regional extension of disease (Stage II) are included.

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MATERIALS AND METHODS

Forty-one patients with biopsy-proved non-Hodgkin lymphoma were referred to the radiation therapy service at Rush-Presbyterian-St Luke's Medical Center between 1960 and 1970. Table II lists a breakdown by pathologic diagnosis. Seventeen cases were classified as lymphosarcoma (LSA), fourteen as reticulum cell sarcoma (RCS), and ten as giant follicular lymphoma (GFL).

Although staging in most instances was retrospective, a modification of the Rye

TABLE I

COMPARATIVE RESULTS IN THE TREATMENT OF MALIGNANT LYMPHOMAS

1945–1971

AUTHORS (Ref.)	YEAR	STAGE*	FIVE-YEAR SURVIVAL NO. OF CASES	FIVE-YEAR SURVIVAL PER-CENT
Craver[1]	1947	—	308	26.3
Stout[2]	1947	—	119	23.5
Hare et al.[3]	1948	—	181	28.7
Hamann[4]	1948	—	43	12.
Lenz et al.[5]	1950	—	242	27.
Nichols et al.[6]	1957	—	71	25.5
Hilton, Sutton[7]	1962	—	65	29.
Cook et al.[8]	1960	I	127	33
		II	84	22.6
Peters[9]		I	102	50.
		II	174	23.
Scheer[10]	1963	I(LSA)	77	75.
		I(RCS)	53	60.
Lipton, Lee[11]	1971	I	20	85.

*Staged according to Rye classification.

classification was used after 1967 (Table III). It should be noted that not all patients had lymphangiograms or bone marrow examinations.

All patients were treated by supravoltage radiation therapy using Cobalt-60. A minimum dose of 3,000 rads in three weeks for a nominal single dose equivalent of 1100 rets, up to 4,000 rads in four weeks for a nominal single dose equivalent 1,320 rets was given. Therapy was administered to a generous treatment volume including the area of involvement and adjacent nodal groups. Patients who developed persistent disease either in the treatment volume or in distant sites were considered treatment failures. In addition, all patients who were lost to follow-up were considered as failures. In Table IV is listed the site of primary or initial involvement. Ten of forty-one (25 percent) showed initial involvement in an extranodal site, the remaining 75 percent were confined to lymph node groups.

TABLE II

NUMBER OF PATIENTS 1960–1970

Lymphosarcoma	17
Reticulum Cell Sarcoma	14
Giant Follicular Lymphoma	10
TOTAL	41

TABLE III

CRITERIA OF STAGING

Stage I — Disease limited to one anatomic region or two contiguous regions on the same side of the diaphragm.

Stage II—Disease in more than two anatomic regions or two noncontiguous regions on the same side of the diaphragm.

TABLE IV

PRIMARY OR INITIAL SITE

1. Cervical lymph nodes	11
2. Inguinal lymph nodes	5
3. Nasal cavity and maxillary antrum	4
4. Axillary lymph nodes	3
5. Submandibular lymph nodes	3
6. Gastrointestinal tract	3
7. Parotid gland	3
8. Supraclavicular lymph nodes	2
9. Tonsil	2
10. Mediastinal lymph nodes	2
11. Nasopharynx	1
12. Orbit	1
13. Pelvic lymph nodes	1
TOTAL	41

Lymphosarcoma

Of seventeen patients classified histologically as lymphosarcoma, fifteen were Stage I and two Stage II according to previously defined criteria. General characteristics of this group are outlined in Table V. Age ranged from 12 to 80 years,

TABLE V

LYMPHOSARCOMA

Patient	Age	Primary Site	Stage	Lymphan-giogram	Bone Marrow	Time of Recurrence	Site of Recurrence
M.D.	12	Left neck	I	None	Normal	1 month	neck & stomach, bone marrow.(died of disease 12/69)
J.W.	40	Right neck	I	Normal	None	(7 yrs. NED)*	
I.P.	48	Neck and nasopharynx	II	Done 1/69 after radiation	Normal	4 months	rt. axilla & para-aortic nodes
D.P.	57	Submandibular	I	None	Normal	(2 yrs. NED)	
B.C.	78	left supraclavicular lt. upper lid & orbit	II	None	Normal	(6 yrs. NED)	
W.G.	18	Jejunum & messentary	II	None	Normal	6 months	site of previous surgery bone marrow
V.F.	58	Left groin	I	Normal	Normal	(4 yrs. NED)	
B.M.	76	Rt. supraclavicular	I	None	None	2 years	left frontotemporal region
J.M.	18	Neck	I	None	None	(10 yrs. NED)	
E.G.	71	Right groin	I	None	None	(4 yrs. NED)	
C.G.	33	Lt. submandibular	I	Normal	Normal	(5 yrs. NED)	
R.H.	53	Pelvic mass displacing bladder	I	None	None	(7 yrs. NED)	
W.M.	26	Left nostril	I	None	None	(4 yrs. NED)	
D.T.	49	Right neck	I	Normal	Normal	(5 yrs. NED)	
N.C.	45	Left nostril	I	None	None	(10 yrs. NED)	
D.B.	80	Epiglottis and rt. false cord	I	None	None	(5 yrs. NED)	died of cerebral hemorrhage
L.S.	73	Right parotid	I	None	None	(2 yrs. NED)	

*No evidence of disease.

the majority of patients falling between the fourth and sixth decade of life. Twelve of seventeen patients were male. Only four patients had a lymphangiogram; only eight had a bone marrow examination. Therapy failed in five patients in this group. Only one had had prior lymphangiography. This patient failed in the retroperitoneal area. Subsequent review of the lymphangiogram showed equivocal enlargement of lymph nodes. In Table VI, it can be seen that thirteen out of seventeen patients available for review at 24 months were free of disease. Eleven of eighteen available for evaluation at 36 months were also free of disease. Ten patients were available for assessment at five years, and eight of these or 80 percent had no evidence of disease at the end of this period.

TABLE VI

LYMPHOSARCOMA

No. Months at Risk	No. of Patients	No. of Patients Free of Disease	Percent Surviving Free of Disease
12 or more	17	14	82
24 or more	17	13	76
36 or more	14	11	78
48 or more	10	8	80
60 or more	10	8	80
72 or more	8	7	87

Reticulum Cell Sarcoma

Fourteen patients are included in this category. Eight were Stage I and six were Stage II. Ages ranged from 16 to 81 years. The majority were in the fourth and fifth decades of life. Eleven of fourteen were male. In Table VII, the general characteristics of this group are defined. Eight of fourteen patients available for review at 24 months were free of disease (Table VIII). Of ten patients available for review at five years, seven or 70 percent have survived free of disease. Of the patients who failed, only one had had a bone marrow aspiration.

TABLE VII

RETICULUM CELL SARCOMA

Patient	Age	Primary Site	Stage	Lymphan-giogram	Bone Marrow	Time of Recurrence	Site of Recurrence
D.G.	46	Nasal cavity & maxillary antrum	II	None	Normal	1 month	Right axilla & skin of chest wall
J.G.	48	Right neck & tonsil	II	Normal	None	1 month	Retroperitoneal nodes & lymph
E.B.	56	Nasal cavity & maxillary antrum	II	None	None	3 months	Right Tonsil (died 1/1 with retroperitoneal lymph)
C.C.	81	Left tonsil	I	None	None	(5 yrs. NED)	
C.F.	68	Stomach	II	None	Normal	Lost to Follow-up	
J.D.	43	Left neck & left axilla	II	Normal	None	(7 yrs. NED)	
F.L.	65	Submandibular	I	None	None	19 months	Left axilla
F.S.	70	Mediastinum	I	None	Normal	Lost to Follow-up	
R.F.	52	Right inguinal	I	Normal	None	(5 yrs. NED)	
J.A.	16	Mediastinum	I	None	Normal	(10 yrs. NED)	
S.N.	55	Left groin	I	None	None	(5 yrs. NED, then lost to Follow-up)	
J.D.	65	Tonsil	I	None	None	9 years	Stomach (died with liver involvement)
K.S.	50	Right parotid	I	None	Normal	(11 yrs. NED)	
H.H.	45	Right neck & tonsil	II	Normal	Normal	(2 yrs. NED)	

TABLE VIII

RETICULUM CELL SARCOMA

No. Months at Risk	No. of Patients	No. of Patients Free of Disease	Percent Surviving Free of Disease
12 or more	14	8	58
24 or more	14	8	58
36 or more	10	7	70
48 or more	10	7	70
60 or more	10	7	70
72 or more	7	5	71

Giant Follicular Lymphoma

In Table IX, the general characteristics of the group with giant follicular lymphoma are outlined. Seven of the patients were Stage I and three were Stage II. The age incidence predominated in the sixth and seventh decades of life. Sex distribution was equal. Only one half the patients had lymphangiography or bone marrow examination, or both, prior to the first course of therapy. In

TABLE IX

GIANT FOLLICULAR LYMPHOMA

Patient	Age	Primary Site	Stage	Lymphan-giogram	Bone Marrow	Time of Recurrence	Site of Recurrence
F.S.	66	Left supraclavicular	I	Normal	Normal	(4 yrs. NED)	
L.G.	58	Left neck, right axilla	II	None	Myelogen-ous leukemia	(2 yrs. NED)	
R.W.	20	Left axilla	I	None	None	(9 yrs. NED)	
G.R.	69	Left axilla	I	Normal	Normal	(3 yrs. NED)	
E.H.	69	Left neck	I	None	None	(4 yrs. NED)	
N.H.	60	Small bowel	II	None	None	6 years	Left supraclavicular
S.M.	55	Left axilla	I	Normal	Normal	(7 yrs. NED)	
R.N.	41	Neck & mediastinum	II	Normal	None	7 years	Palpable disease rt. neck Lymphangiogram para-aortic nodes
E.S.	49	Left neck	I	Normal	Normal	6 months	Inguinal
H.D.	50	Right neck	I	Normal	Normal	(2 yrs. NED)	

Table X, one can readily observe that two years after therapy, the failure rate levels out and that within the next three or four years, additional failures are not seen. Eight of nine patients available for review at 24 months are free of disease as are three of four patients available for review at five years.

TABLE X

GIANT FOLLICULAR LYMPHOMA

No. Months at Risk	No. of Patients	No. of Patients Free of Disease	Percent Surviving Free of Disease
12	10	8	80
24	9	9	89
26	7	7	86
48	6	5	83
60	4	3	75
72	4	3	75

DISCUSSION

While the numbers in this review do not provide an adequate sample for statistical comparisons, improvement in survival figures reported by others undoubtedly reflect the development of more precise methods of staging and improved methods of treatment. It is current practice to employ chest roentgenography, intravenous urography, lymphangiography, bone marrow aspiration, and isotopic scanning of liver and spleen to define extent of disease prior to treatment. In several centers, laparotomy, splenectomy, wedge liver biopsy and lymph node biopsy have been introduced to define extent of disease even more precisely.

Permanent local control of disease can generally be achieved by supravoltage radiation therapy. Although Seydel et al.[12] suggests that 2,000 rads in two weeks may be adequate to control giant follicular lymphoma, we feel that a total dose of 3,000 rads in three weeks should be given for all histologic types. This dose should be delivered to involved lymph nodes and adjacent uninvolved lymph node groups with an additional 500 rads to the involved area. Peters[9] has shown that radically extended treatment fields are not indicated in the non-Hodgkin lymphomas.

Optimal treatment of lymphomas will not be defined adequately until staging methods have been refined to a point where the disease can be precisely staged. Until this is achieved, the combination of chemotherapy and local radiation therapy may improve survival figures still further. Studies of this type are now in progress.

SUMMARY

The excellent results currently being obtained in the treatment of non-Hodgkin lymphomas have been overshadowed by the astonishing success achieved in the treatment of Hodgkin's disease. We have attempted in this article to contribute further to the literature which is accumulating with regard to non-Hodgkin lymphomas, emphasizing the necessity to thoroughly evaluate and stage these diseases initially, and to follow this with appropriate curative therapy.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Bacteriology

Edwards LD, Balagtas R, Lowe P, Levin S, Lepper MH, Landau W, Kallick C: An analysis of ordering patterns and utilization of bacteriology culture reports. *Presented at the 53d Ann Session of the Amer Coll of Phys, 1972*

A two week period prevalence study was conducted to determine ordering patterns and utilization of bacteriology reports.

All bacteriology reports (1381) were monitored, and ongoing chart review was conducted on all new inpatients (436) who had cultures taken.

Seventeen percent of infections were not cultured when indicated. Total laboratory costs to the patients were $15,364, or an average of $11.12 per culture. Cultures ordered for suspected infections (1286) yielded 979 (76.1 percent) negative results (no growth, contaminants, normal flora, or light growth of pathogens) and 307 (23.9 percent) positive results (significant growth of pathogens). Ninety-five follow-up cultures were ordered for known infections. One-third of the time, when cultures were taken the patients were on antimicrobials. Immediate gram stains were performed 38 times. Empiric treatment was initiated after the culture was taken in 11.5 percent. After availability of culture results, antimicrobial therapy was changed 14 times and initiated 65 times. Of 410 significant isolates therapeutic coverage was obtained on 132 (32.2 percent) before and 175 (42.7 percent) after availability of results (treatment was discontinued 20 times and added 63 times). Detailed analysis was carried out on 1287 cultures by anatomical site on the medical and surgical services.

Known disparity between *in vitro* sensitivities and *in vivo* results, injudicious selection of patients for culture, improper bedside culture and transport techniques, over-utilization of antimicrobials before cultures were taken, and under-utilization of follow-up cultures on known infections were factors that affected the results reported here. A reappraisal of current clinical bacteriology utilization is indicated.

Biochemistry

Bezkorovainy A, Grohlich D: Maleylation of bovine colostral IgG and human serum IgG. *Immunochemistry 9:137-146, 1972*

Bovine colostral and human serum IgG were maleylated to different degrees to test for the reversibility of the maleylation reaction and the utility of this reaction in the study of the quaternary structure of immunoglobulins. The exhaustively maleylated IgG preparations were reduced-alkylated and the subunits were separated by gel filtration on Sephadex G-200 columns. In both the human and bovine IgG preparations, the sums of two heavy and two light chains accounted for the entire molecular weight of the intact immunoglobulins.

The removal of maleyl groups from intact maleylated bovine IgG was best accomplished at pH 3·5 for 2 days at 37-40°C. The yield of the de-maleylated material, which was immunochemically and ultracentrifugally identical to authentic IgG, was only 30 per cent.

The rest was not soluble at neutral pH values. The yield of soluble material was larger if the reaction was carried out at pH 2·2; however, fragmentation of the protein was noted under these conditions. The removal of a substantial number of maleyl groups from the maleylated subunits of IgG preparations could be accomplished only by a combination of a pH 2·2 hydrolysis at 40°C for 5 days and treatment with hydroxylamine. No significant fragmentation of the subunits took place under these conditions.

Booyse FM, Hoveke TP, Kisieleski D, Rafelson ME Jr: Mechanism and control of platelet-platelet interactions: II. Action of thrombin on membrane-associated and purified platelet and rabbit skeletal muscle myosins. *Microvasc Res 4:199-206, 1972*

Thrombin action on intact human platelets was studied using SDS-acrylamide gel electrophoresis. Analysis of purified platelet membranes from thrombin-treated intact platelets showed the rapid disappearance of a peptide with a molecular weight of 200,000 and the simultaneous appearance of three smaller peptides with molecular weights of 171,000, 85,000, and 78,000. Isolated human platelet myosin is degraded by thrombin to peptides identical with those produced in platelet membranes. ATPase activity was retained in the thrombin-cleaved platelet myosin fragments and these fragments also contained peptides similar to rabbit heavy meromyosin. Thrombin produced similar changes in rabbit skeletal muscle myosin. We conclude that the thrombin-sensitive protein of platelet membranes is identical with isolated platelet myosin and that thrombin action produces heavy meromyosin-like and possibly light meromyosin-like fragments.

Booyse FM, Hoveke TP, Kisieleski D, Rafelson ME Jr: Mechanism and control of platelet-platelet interaction: I. Effects of inducers and inhibitors of aggregation. *Microvasc Res 4:179-198, 1972*

With the technique of shadow-casting of whole platelets, it has been possible to observe both the very early events produced on the platelet surface by aggregating agents and what appears to be the entire process of platelet aggregation. It has been shown that a variety of aggregating agents and conditions such as ADP, thrombin, collagen, polylysine, glass and cold induce a common sequence of reactions leading to aggregation. The data presented here show that the platelet membrane does not directly participate in the early events preceding and leading to platelet aggregation. It is extruded platelet cytoplasm (cytogel) that appears to interact to form interplatelet attachment. Subsequent platelet membrane interactions appear to follow the contraction of the interacted cytogels which brings the platelets into close contact. The action of several inhibitors of aggregation have been localized to specific steps in the sequence of events observed.

Booyse FM, Rafelson ME Jr: Mechanism and control of platelet-platelet interactions: III. A relaxation-contraction model for platelet aggregation. *Microvasc Res 4:207-213, 1972*

A model for platelet aggregation is proposed in which the triggering of the very early events preceding and leading to aggregation is due to the direct action of aggregating agents (ADP, thrombin, collagen, etc.) on a surface or membrane-localized thrombosthenin that exists in a contracted state. Relaxation of this membrane ATPase (platelet activation) with subsequent loss of membrane permeability control is followed by: extrusion of platelet cytoplasm (cytogel) containing thrombosthenin in a relaxed state; interaction of the

extruded cytogels; and contraction and retraction of the interacted cytogels drawing the platelets together. Interaction of the extruded cytogels is viewed as simply being the result of protein-protein interactions and contraction is conceived as resulting from the contact of the cytogels with the ionic environment of the plasma.

Chiao MT, Bezkorovainy A: Interaction of modified haptoglobin with hemoglobin. *Biochim Biophys Acta 263:60-69, 1972*

Human haptoglobin was modified with various group-specific reagents, and the function of the modified side-chains in the binding of hemoglobin was investigated using the peroxidase, rivanol, and starch-gel electrophoresis methods. Nitration of the tyrosyl groups of haptoglobin resulted in the loss of its hemoglobin-binding activity as well as its typical polymorphism in the starch-gel electrophoresis system without an apparent randomization of the conformation. Histidyl and carboxyl groups of haptoglobin were not involved in the binding of hemoglobin. Modification of the lysyl residues by reductive alkylation did not result in the loss of the hemoglobin-binding activity of haptoglobin, though trinitrophenylation and maleylation of haptoglobin was accompanied by the loss of its biological activity. However, the possibility that the effects of these procedures were due to a non-specific alteration of the conformation of haptoglobin has not been rigorously excluded. It was concluded that the tyrosyl groups of haptoglobin remain the sole hemoglobin-binding ligands of haptoglobin, whose role in this reaction is reasonably certain. The role of the imidazole groups of hemoglobin in the reaction with haptoglobin could not be confirmed by carboxymethylation.

Cardio-respiratory

Rossof AH: An electrocardiographic study of the giraffe. (*Letter to the Editor*) *Amer Heart J 83:142, 1972*

An electrocardiogram (ECG) was obtained in an anesthetized female reticulated giraffe (*giraffa camelopardalis reticulate*). Its characteristics are analyzed and compared with the ECG's of other ungulates and with carnivores and primates.

Schoenberger JA, Eckenfels EJ, Knott AP, Lepper MH: Evaluation of mass community screening for hypertension in an urban ghetto. *Presented at the Conf on Cardiovasc Dis of the Amer Heart Assoc, Tampa, Fla, Feb 1972*

The recent ICHD report on hypertension emphasized the need for effective methods of detection and referral of hypertensives especially in the urban ghetto, where these problems are acute. This study used mass community screening for case-finding and referral in an urban ghetto with a free health center. A dwelling unit count and household enumeration conducted during the screening resulted in a population estimate of 18,619. The U.S. Census reported 22,815 area residents. A comparison showed the average household occupancy and proportion of total population by tract were almost identical in both censuses. Recounts of dwelling units in select tracts offer strong evidence of an over-estimation by the U.S. Census.

Casual blood pressures were taken on 12,438 persons in their homes, or 72 percent of the adjusted population at risk. Fifteen hundred, fifty-four hypertensives were found; the prevalence rate for those between 18 and 79 years was 23.5 percent. Door-to-door screening

was most successful in the housing projects and least successful in areas of high deterioration.

Hypertensives were classified according to awareness and treatment. Of the 35 percent on therapy only 42 percent were normotensive; and of the 47 percent unaware hypertensives almost two-thirds received no care whatever. Eighteen percent were aware of their condition but not treated. Sixty-three percent of the males and 39 percent of the females were unaware of their condition, whereas 40 percent of the females and 24 percent of the males were under treatment.

Over one-third of the hypertensives did not respond to follow-up, of which two-thirds could not be located on return visits. Nevertheless, half of those who were unaware of their condition were reached by the follow-up, including 35 percent of those receiving no care whatever. The most responsive to follow-up were the elderly female health center users residing in the housing projects. The most difficult to reach on follow-up were the young and middle-aged males, unemployed or unskilled workers, living in the areas of condemned or torn down housing.

Mass hypertension screening can be effective in reaching hypertensives in the urban ghetto and offers the neighborhood health center an opportunity to better understanding their own system.

Gastro-enterology

Brown H, Hardison WGM: Fluorocarbon sonicated as a substitute for erythrocytes in rat liver perfusion. *Surgery 71:388-394, 1972*

Sonicated fluorocarbon was used as an erythrocyte substitute for perfusion of rat livers. When perfused with sonicated fluorocarbon in 5 percent albumin solution, rat liver initially functioned better than liver perfused with albumin solution alone but not as well as liver perfused with rat whole blood. Portal pressure rose after two to three hours of perfusion in livers perfused with fluorocarbon. Microscopic studies showed ballooning of hepatic sinusoids. Further, restriction in distribution of perfusion was indicated by India-ink injection studies. Vascular damage principally in capillary walls is believed responsible for progressive vascular occlusion and ballooning of sinusoids in the liver, ultimately causing poor perfusion and poor metabolic function. If vascular damage can be avoided by judicious use of platelets or their derivatives, fluorocarbon may be more suitable for liver perfusion and preservation experiments, since it is capable of delivering as much oxygen to the tissue as erythrocytes.

Hardison WGM, Apter JT: Micellar theory of biliary cholesterol excretion. *Amer J Physiol 222:61-67, 1972*

The relation between biliary bile salt excretion and biliary cholesterol and phospholipid excretion was studied in bile-fistula rats infused with graded doses of bile salt. With infusion of taurocholate, a micelle-forming bile salt, increase in biliary bile salt excretion was associated with an increase in biliary lipid excretion. With infusion of dehydrocholate, a nonmicelle-forming bile salt, biliary lipid excretion increased little. With taurocholate infusion, the relation between biliary bile salt and lipid excretion was not linear. At high bile salt excretion rates, biliary lipid excretion rate increased little in spite of increasing biliary bile salt excretion rate. At very low bile salt and phospholipid excretion rates, cholesterol excretion remained disproportionately high. At low infusion rates therefore, bile was more nearly saturated or supersaturated with cholesterol than at high rates. Micelle formation appears an important mechanism in biliary lipid excretion, but it alone cannot explain the quantitative relation between biliary bile salt and lipid excretion.

Gewurz H: Interaction between lipopolysaccharides (LPS) and the complement (C) system: Solubilization of C-consuming substances during brief absorbtions at 0^{01} (*35311*). *P.S.E.B.M. 136:561-564, 1971*

Attempts were made to remove antibodies and other serum factors involved in the interaction between endotoxic lipopolysaccharides (LPS) and the complement system by brief absorptions of guinea pig serum with LPS at 0°. However, in addition to removal of serum factors, this procedure also resulted in the solubilization or "imbibation" of LPS constituents into the fluid phase, such that when the absorbed sera were subsequently incubated at 37°, or hyperimmune rabbit anti-LPS serum was added to them at either 0 or 37°, LPS constituents which initiated C consumption were found. C consumption upon addition of LPS to absorbed sera persisted, even as bactericidal activity against the parent *Veillonella* organisms was reduced. While the importance of solubilization of LPS to its interaction with the C system is not yet known, these experiments show the difficulty of evaluating the factors in serum which initiate C consumption upon addition of LPS and their relationship to "natural" bactericidal antibodies.

Johnson D, Gewurz H, Moberg AW, Simmons RL, Najarian JS: Reactivities to horse anti-lymphocyte globulin. III. The induction of immunologic paralysis to horse γ-globulin (HoGG) and anti-lymphocyte globulin (HoALG) in adult rabbits. *Int Arch Allergy 40:789-805, 1971*

The immune response of adult rabbits to daily doses of horse γ-globulin (HoGG) administered intravenously or intramuscularly in various tolerance-inducing regimens was investigated. Circulating HoGG, anti-HoGG antibodies, and hemolytic complement (C) levels were measured daily. High dose tolerance, as defined by antigen elimination, was achieved by both routes with 100, but not 10, mg HoGG/kg body weight/day. There was an initial accumulation of large amounts of HoGG during the first week. The HoGG titer decreased markedly during weeks two and three in association with the appearance of agglutinating and precipitating anti-HoGG antibody in most of the animals. However, by the fourth week detectable antibody formation against certain of the HoGG antigens ceased and the HoGG concentration again began to rise. Antibodies to at least one HoGG antigen persisted while "tolerance" to at least two other HoGG antigens has been induced. Serum C levels showed close correlation with HoGG levels, such that marked hypocomplementemia was seen during the immune phase of weeks two and three, and normal elevated C levels were observed when HoGG levels rose to the high "tolerant" values. Pretreatment with centrifuged deaggregated HoGG seven days prior to the daily regime led to accumulation of each of the three HoGG antigens without a demonstrable immune phase; antigen levels constantly were high, circulating antibodies could not be detected and hypocomplementemia was avoided. Administration of horse anti-rabbit lymphocyte serum in association with HoGG led to a greatly increased catabolism of the HoGG, an early appearance of anti-HoGG antibodies and absence of tolerance to any HoGG antigens. These observations add descriptive data on the interplay between antigen, antibody and C during the induction of high-dose tolerance, and have aided in interpreting the response of humans to HoGG and horse anti-lymphocyte globulin (HoALG). They are consistent with the hypothesis that dosages of HoGG commonly used in the administration of HoALG to man favor the induction of tolerance to HoGG via the mechanism of "immunologic paralysis" or "high-dose tolerance."

Moberg AW, Shons AR, Gewurz H, Mozes M, Najarian JS: Prolongation of renal xenografts by the simultaneous sequestration of performed antibody, inhibition of complement, coagulation and antibody synthesis. *Trans Proc 3:538-541, 1971*

The effect of antibody absorption, C and fibrinogen depletion on the survival of pig xenografts in dogs was determined. Hyperacute rejection was initiated by deposition of preformed antibodies on donor endothelium; the ensuing complex reaction was mediated by C, clotting activation and vasospasm. Simultaneous antibody absorption and complement depletion were the most effective in inhibiting the rapid rejection. Complement depletion eliminated the vasoactive component of rejection; inhibition of this major effector system produced moderate prolongation. Coagulation activation occurred principally as a secondary response to antibody disposition, and was not a primary effector mechanism. Fibrinogen depletion did not give prolongation. Cytosine arabinoside did not decrease antibody synthesis of preformed antibody when given prior to transplantation, in conjunction with antibody adsorption.

Oncology

Malkinson FD, Griem ML, Marianovic R: Follicle Squash Preparations: Uses in studies of cell kinetics following irradiation. *J Invest Derm 57:382-388, 1971*

These investigations in CF_1 mice were undertaken to establish the usefulness of whole follicle squash preparations in kinetics studies of anagen matrix cell responses to ionizing radiation. The backs of mice were plucked and H^3TdR (0.8 uCi/g) was injected intraperitoneally 15 minutes prior to irradiation. Animals were treated with 100 rads at 45 kv. Skin biopsies were fixed in cold acid alcohol for 24 hours, brought through graded alcohols to water, hydrolyzed in 1N HCl, and transferred to Schiff's reagent overnight. Individual follicles were dissected free and squashed on slides in 45 percent acetic acid. Auto-radiographs were made from squash preparations.

Mitotic indices were reduced within 30 minutes after x-ray exposure (2.4 percent in control sites vs 1.8 percent in irradiated sites) and dropped sharply after two hours (2.2 percent vs 0.7 percent). There was essentially complete recovery of the mitotic index within seven hours after irradiation (2.1 percent vs 1.7 percent). The post-radiation G_2 period delay was one and one-half to two hours. Studies of the four individual hair types revealed no significant differences in radiation responses despite substantial differences in the sizes of matrix cell populations. Usefulness of the techniques described for kinetics studies of drug or radiation effects on proliferative cell populations is emphasized.

Pathology

Sorgente N, Eisenstein R, Kuettner KE, Hascall V: The association of cartilage lysozyme with matrix components. *Presented at the 18th ann meeting of the Orthopaedic Res Soc Washington, D.C. Jan, 1972*

Lysozyme, a cationic protein, has been identified in cartilage as a component of the extracellular matrix, localized primarily in the lacunar space of the matrix. Since, in mammalian tissues, no substrate has been found, it seemed likely that it is a structural component,

probably associated with the strongly anionic proteoglycans. Various methods were therefore devised to test whether or not the lysozyme molecules interact with the cartilage proteoglycans. The data presented show that the proteoglycans and lysozyme do not interact in the tissue, and suggest that some other component(s) of the matrix, probably glycoprotein in nature, is complexed with lysozyme in the tissue.

Virology

Deinhardt F: Use of marmosets in biomedical research. Med Primatol, 1970. *Proc 2nd Conf Exp Med Surg Primates, New York, 1969, pp. 918-925*

The history and reasons for the establishment of marmoset monkey experimental and breeding colonies are reviewed, and the use of marmosets in studies of human infectious hepatitis and tumor viruses is described.

Falk LA, Wolfe LG, Deinhardt F: Herpesvirus Saimiri (HVS): Incidence of latent infection in squirrel monkeys. *Fed Proc 31:806, Mar-Apr 1972*

HVS, oncogenic for some species of South American primates, exists latently and apparently causes no overt disease in the natural host, squirrel monkeys (SM). The incidence of latent HVS infection in two colonies of SM was studied by: isolation of HVS from blood obtained from healthy SM and evaluation of HVS serum antibody levels by indirect fluorescent antibody methods. By cocultivation of whole blood (WB) or peripheral lymphocytes (PL) with susceptible cells, HVS was isolated from 63 of 139 (45%) SM, but attempts to isolate virus from cell-free extracts of WB and PL failed. HVS was isolated from SM more than two months old but not from five younger SM and only 30% of animals less than one year of age had HVS antibodies, whereas 100% of animals more than two years old had antibodies with peak titers of 1:128. Both of these findings suggest horizontal transmission of HVS early in life. Cotton-topped and white-lipped marmosets, experimentally infected with one of the viruses isolated from WB of healthy SM, developed a lymphoproliferative disease and survived 18 to 26 days PI. The gross and microscopic features of the neoplastic disease were indistinguishable from those produced by the prototype strain of HVS.

Falk LA, Wolfe LG, Marcynska B, Deinhardt F: Characterization of lymphoid cell lines established from herpesvirus saimiri (HVS)-infected marmosets. *Bacteriol Proc. 1972*

Concentrated suspensions of neoplastic cells were obtained by Ficoll-Hypaque gradients from trypsinized lymphoid organs (lymph nodes, spleen and thymus) and from peripheral blood of cotton-topped and white-lipped marmosets with herpesvirus saimiri (HVS)-induced lymphomas and lymphocytic leukemias. Using such cell suspensions, six lymphoid cell lines have been established and have been serially propagated up to eight months in cell culture. Four of the cell lines grow in suspension as single cells and clumps of cells, one cell line grows as a monolayer with many free floating cells and one line grows only as a monolayer. Infectious HVS has been continually recovered from all the lymphoid cell lines by cocultivation of the cells with susceptible indicator cells, and several months after the cultures were initiated very small amounts of infectious HVS also was recovered intermittently from supernatants of the cell lines. HVS-associated antigens were demonstrable in 0.1 percent of the cells by indirect fluorescent antibody methods. No specific chromosomal

aberrations have been observed in the cell lines after seven months cultivation. Electron microscopic studies and cloning experiments with the lymphoid cell lines are in progress.

Falk LA, Wolfe LG, Hoekstra J, Deinhardt F: Demonstration of *herpesvirus saimiri*-associated antigens in peripheral lymphocytes from infected marmosets during *in vitro* cultivation. *J Nat Cancer Inst 48:523-530, Feb 1972*

Peripheral lymphocytes from white-lipped (*Saguinus fuscicollis and S. Nigricollis*) marmosets infected with *Herpesvirus saimiri* (HVS) were separated from whole blood on Ficoll-Hypaque gradients. The cells were cultivated *in vitro* in suspension or with susceptible vero cells (a continuous line of African green monkey kidney cells) and were examined for infectious HVS and HVS-associated antigens. HVS antigens were not demonstrated in smears of lymphocytes immediately after removal from the marmosets, but lymphocyte smears examined after 24, 48 and 72 hours' cultivation showed that 1 to 5 percent of the lymphocytes contained stainable HVS antigens. Infectious HVS was not recovered from supernatants or cell-free extracts of lymphocyte suspensions after cultivation up to 120 hours, and herpes-type particles were not seen by electron microscopy in lymphocytes cultured up to 72 hours. HVS antigens developed in lymphocytes 24 hours after cocultivation with vero cells, and already a small percentage of lymphocytes had transferred the HVS genome in some form to the vero cells. HVS was recovered from supernatants and cell-free extracts of cocultivation cultures 48 to 72 hours after incubation.

Massey RJ, Johnson TR, Deinhardt FW: Lymphocyte and antibody tumor cell cytotoxicity measured by a micro ^{51}CR release assay. *Fed Proc 31:767, 1972. Abstract.*

Previously described lymphocyte and antibody cytotoxicity assays, based on ^{51}Cr release from target cells, require 2.5 x 10^4 to 1.0 x 10^5 labeled target cells and as many as 1 x 10^7 lymphocytes per test. A micro assay was developed using 1 x 10^4 ^{51}Cr labeled target cells with lymphocytes in lymphocyte to target cell ratios of 25:1 to 100:1, or with 25λ of serial twofold serum dilutions plus 50λ of complement. Plates were incubated at 37°C for four hours (lymphocytotoxicity) or two hours (serum cytoxicity) and the specific release of ^{51}Cr was determined. Marmoset skin and muscle cells, obtained by biopsy, were transformed *in vitro* with Rous sarcoma virus, feline sarcoma virus or simian sarcoma virus type 1. Transformed cells were inoculated into the animal from which the original tissue had been obtained and lymphocyte or serum mediated cytotoxicity *vs* the transformed but not *vs* the normal autochithonous skin and muscle cells were measured. Preliminary data indicate that the assay can also be used to measure the cellular and humoral response of human tumor patients.

McDonald R, Wolfe LG, Deinhardt F: Feline fibrosarcoma virus: Quantitative focus assay, focus morphology and evidence for a "helper virus." *Int J Cancer 9:57-65, 1972*

Feline fibrosarcoma virus (FeSV) was assayed by focus formation in feline and marmoset fibroblast cultures overlaid with agar and re-fed with fluid media. The FeSV titers were consistent from experiment to experiment and were about four times higher in feline fibroblasts than in marmoset fibroblasts in parallel assays. Clones of FeSV-infected cells grown in soft agar, and foci of transformed cells produced by FeSV in monolayer cell cultures were both of two morphological types: round cells (r) and a loose meshwork of fusiform and round cells (fr). Thermal stability experiments indicated that the morphological differences of the foci were virus-dependent.

The titration pattern of FeSV grown in marmoset or feline cells indicated that these preparations were either competent or contained an excess of helper virus. Preliminary challenge experiments with Snyder-Theilen FeSV grown in marmoset cells indicated that a 10- to 100-fold excess of non-transforming, interfering virus (helper virus) was present in this FeSV preparation.

Smith RD, Wolfe LG, Deinhardt F: Pathology of tumors induced in marmosets with feline fibrosarcoma virus. *Amer J Path 62:84a-85a, 1971*

Inoculation of eight newborn marmoset monkeys with cell-free extracts from two cat fibrosarcomas resulted in the development of invasive sarcomas in six marmosets. Tumors contained a mixture of spindle and polygonal cells and scant amounts of collagen. In addition to metastases in lymph nodes and lung, regional lymph nodes contained histiocytic and multinucleated giant cells. By electron microscopy, the neoplasms were composed of atypical fibroblasts and other cells containing abundant lysosomes, but no virus was found in any of the six tumors. However, electron microscopy of tissue culture cells derived from one tumor revealed numerous C-type extracellular and budding virus particles. Inoculation of marmosets with tumor minces from the original marmoset tumors resulted in the rapid development of recipient sarcomas. Although the histology of the sarcomas following repeated marmoset passage remained essentially unchanged, electron microscopy of the second and later passage neoplasms revealed typical virus particles within the tumors. These results indicate that the feline fibrosarcoma virus-induced tumor in the primate may contain the viral genome in an integrated state, but that virus can be readily rescued by tissue culture or repeated tumor passage.

Wolfe LG, Marcynska B, Rabin H, Smith R, Tischendorf P, Gavitt F, Deinhardt F: Viral oncogenesis in nonhuman primates. *Med Primatol 1970, Proc 2nd Conf Exp Med Surg Primates, New York, 1969, pp. 671-682*

Oncogenicity of Rous sarcoma virus in marmoset monkeys was described and compared to several species of Old and New World monkeys and preliminary data on experimental transmission of feline sarcoma virus to marmosets were presented. Marmosets were not susceptible to tumor induction by murine leukemia and sarcoma viruses, feline leukemia virus, Yaba virus, Epstein-Barr virus and selected human tumor tissues.

INTRODUCTION

The clinical presentations of neoplastic processes can be as diverse as the tumors themselves. While many tumors, especially of the integument, are detected by their visual presence, the majority of cancers become clinically evident when they interfere with the proper functions of the organs which harbor them. Occasionally they interfere with adjacent organs. Thus, cancers of the gut obstruct it or bleed into it, bile flow is halted by cancers of the head of the pancreas, brain tumors are associated with neurologic disability, and patients with laryngeal cancer have a hoarse voice.

Uncommonly, however, the presence of a totally unsuspected cancer is heralded by a wide variety of systemic symptoms. This symposium analyzes and discusses, from a clinician's frame of reference, the salient features of these remote effects of neoplasia on the human organism.

Arthur H. Rossof
Charles P. Perlia
GUEST EDITORS

THE REMOTE EFFECTS OF CANCER ON THE NERVOUS SYSTEM: A REVIEW

Robert R. McKendall
Maynard M. Cohen

INTRODUCTION

The purpose of this review is to present a clinically oriented summary of a group of diseases which occur in the nervous system in association with underlying malignancy. We shall define the important syndromes, organize them into a clinically useful and easily remembered classification, indict the most commonly responsible cancers, comment on pathogenesis when clearly documented, and report important therapeutic concepts where they exist. Special stress will be placed on those conditions which may precede or herald the appearance of a tumor—such as myasthenia gravis, Eaton-Lambert syndrome, dermatomyositis, and subacute cerebellar degeneration.

The diseases we shall cover are those which affect the nervous system indirectly. Metabolic derangements in cancer states are perhaps the most common indirect cause of nervous system dysfunction. Hyper- and hypoglycemia, electrolyte imbalance, hypoxia, and water intoxication are well known mechanisms of cerebral dysfunction whether due to a neoplastic or non-neoplastic disease. Only when such abnormalities occupy important places in the differential diagnosis of a specific neurologic syndrome will they be discussed. For more extensive coverage of metabolic states the reader is referred to other articles in this Symposium.

In addition to excluding metabolic abnormalities from our discussion, we have also excluded any lengthy discussion of the direct effects of cancer on the nervous system. Metastatic involvement of the nervous system is overwhelmingly the most common neurologic complication of cancer. One should only entertain a diagnosis of a remote effect of cancer once a patient's clinical presentation and diagnostic workup is incompatible with a diagnosis of metastasis. Metastasis is a common cause and a remote effect is an uncommon cause of nervous system involvement. The subject of metastases to the nervous system has recently been extensively reviewed.[1]

CLASSIFICATION

In few areas of neurology is the terminology more confusing to the non-neurologist than in the descriptions of the manifestations of the remote effects of cancer on the nervous system. Table I

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TABLE I

CLASSIFICATION

I. ENCEPHALOPATHIES
- A. Progressive Multifocal Leukoencephalopathy
- B. Diffuse Polioencephalopathy
  - 1. Encephalomyelitis
  - 2. Subacute Cerebellar Degeneration
- C. Metabolic Encephalopathy

II. MYELOPATHY
- A. Subacute Neurotic Myelopathy
- B. Amyotrophic Lateral Sclerosis

III. PERIPHERAL NEUROPATHY
- A. Pure Sensory Neuronopathy
- B. Mixed Sensorimotor Polyneuropathy

IV. MYOPATHIES AND DISORDERS OF THE NEUROMUSCULAR JUNCTION
- A. Myasthenia Gravis
- B. Eaton-Lambert Syndrome
- C. Polymyositis/Dermatomyositis
- D. Carcinomatous Neuromyopathy

represents an attempt to simplify some of the confusion which has arisen in the literature. It is based primarily on the classification presented in 1965 by Brain and Adams.[2] We feel that its clinical usefulness justifies our simplification.

Non-metastatic involvement of the nervous system can be divided into four categories: (1) the encephalopathies, (2) the myelopathies, (3) the neuropathies and (4) the myopathies. The encephalopathies include multifocal leukoencephalopathy, a disease named for its primary effect on the white matter, and diffuse polioencephalopathy, a disease named for its primary effect on the grey matter. The former is a crisp nosological entity, while the latter is a disease of a more pleomorphic and elusive nature. The myelopathies include two diseases—subacute necrotic myelopathy and amyotrophic lateral sclerosis (ALS). The evidence linking ALS to cancer is inconclusive and hence will not be included in this paper. The neuropathies fall into two major clinical classes—either a pure sensory neuronopathy or the more common mixed sensorimotor neuropathy. Lastly, the myopathies can be divided into those which cause wasting—polymyositis, dermatomyositis, and nonspecific carcinomatous neuromyopathy—and those which do not—myasthenia gravis and the Eaton-Lambert syndrome.

INCIDENCE

The incidence of the various syndromes is difficult to assess accurately and is further complicated by disagreements over classification. One of the largest series available is that of Croft and Wilkinson who examined for evidence of neurologic disease all patients with a diagnosis of cancer who were admitted to the London Hospital from 1960 to 1964. There were 1465 such patients, 96 of whom (6.6 percent) had some form of neurologic deficit.[3] When analyzed according to the type of cancer, the incidence varied from 0.5 percent to 16.4 percent, the highest incidence being found in carcinomas of the ovary, lung and stomach (see Figure 1). Other large series have quoted somewhat lower incidences of 3 to 5 percent. Figure 2 shows the breakdown from the standpoint of which neurologic disease occurs most frequently with a given type of malignancy. Clearly neuromyopathy and peripheral neuropathy are the most frequent neurologic deficits seen in lung, ovary and stomach cancer. Figure 3 analyzes the data from the opposite standpoint. Given a group of patients with a specific neurologic disease and a cancer, which type of carcinoma is most common? Regardless of the type of neuro-

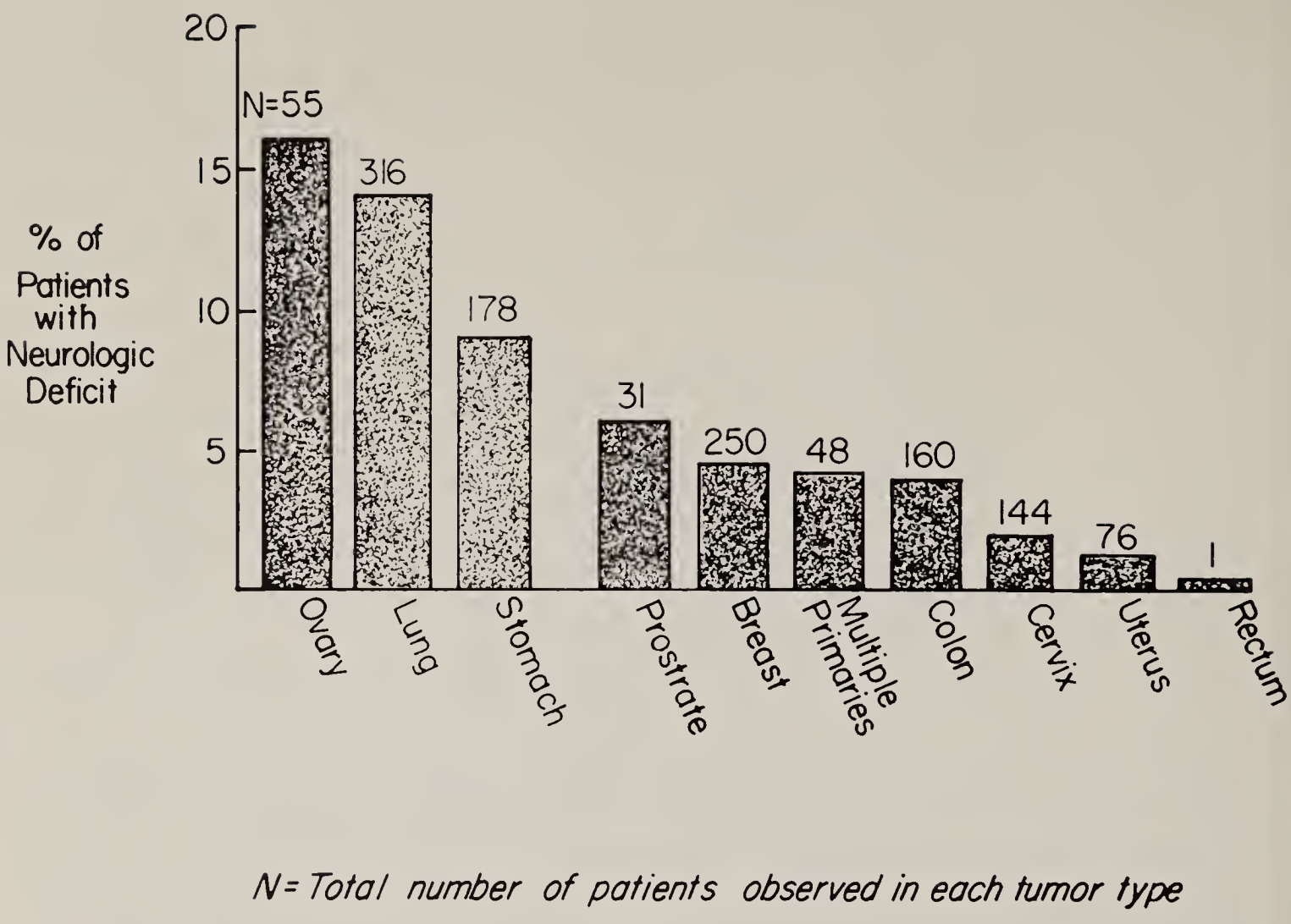

Fig. 1—Incidence of non-metastatic neurologic deficits in 1,465 patients with various types of malignancy (modified from Croft and Wilkinson[3]).

logic deficit, lung cancer stands out as the most prevalent tumor.

In summary then, lung, ovary, and stomach cancers appear to be the only malignancies (excluding the special situation of thymomas) associated with a neurologic deficit more commonly than by chance. The most prevalent neurologic deficit is a peripheral neuropathy or a neuromyopathy. Most patients presenting with a neurologic deficit related to a cancer will have cancer of the lung. The major exception to this generalization is in subacute cerebellar degeneration, in which case carcinoma of the ovary should receive special consideration.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

In 1958 Astrom, Mancall and Richardson[4] reported three new cases and reviewed five previously reported cases of a disease of the central nervous system characterized by widely disseminated foci of demyelination occurring exclusively in a background of chronic debilitating disease. The onset was typically acute or subacute and, once begun, the disease ran a relentlessly progressive course, even in the face of a remission of the patients' underlying disease. For this disease these authors suggested the name progressive multifocal leukoencephalopathy (PML).

The clinical presentation of the disease is as varied as its pathological distribution is widespread. Cerebral symptoms of lethargy, stupor, hemianopsia, hemiplegia, dementia, aphasia, and personality alterations are common. Brain stem symptoms of dysphagia, diplopia, dysarthria, nystagmus, vertigo, and palatal weakness are also prominently represented. Involvement of the cerebellum is less common but cases have been reported in which cerebellar ataxia was the main finding. Basal ganglia symptoms such as dystonia, chorea, and parkinsonian rigidity are infrequent, and

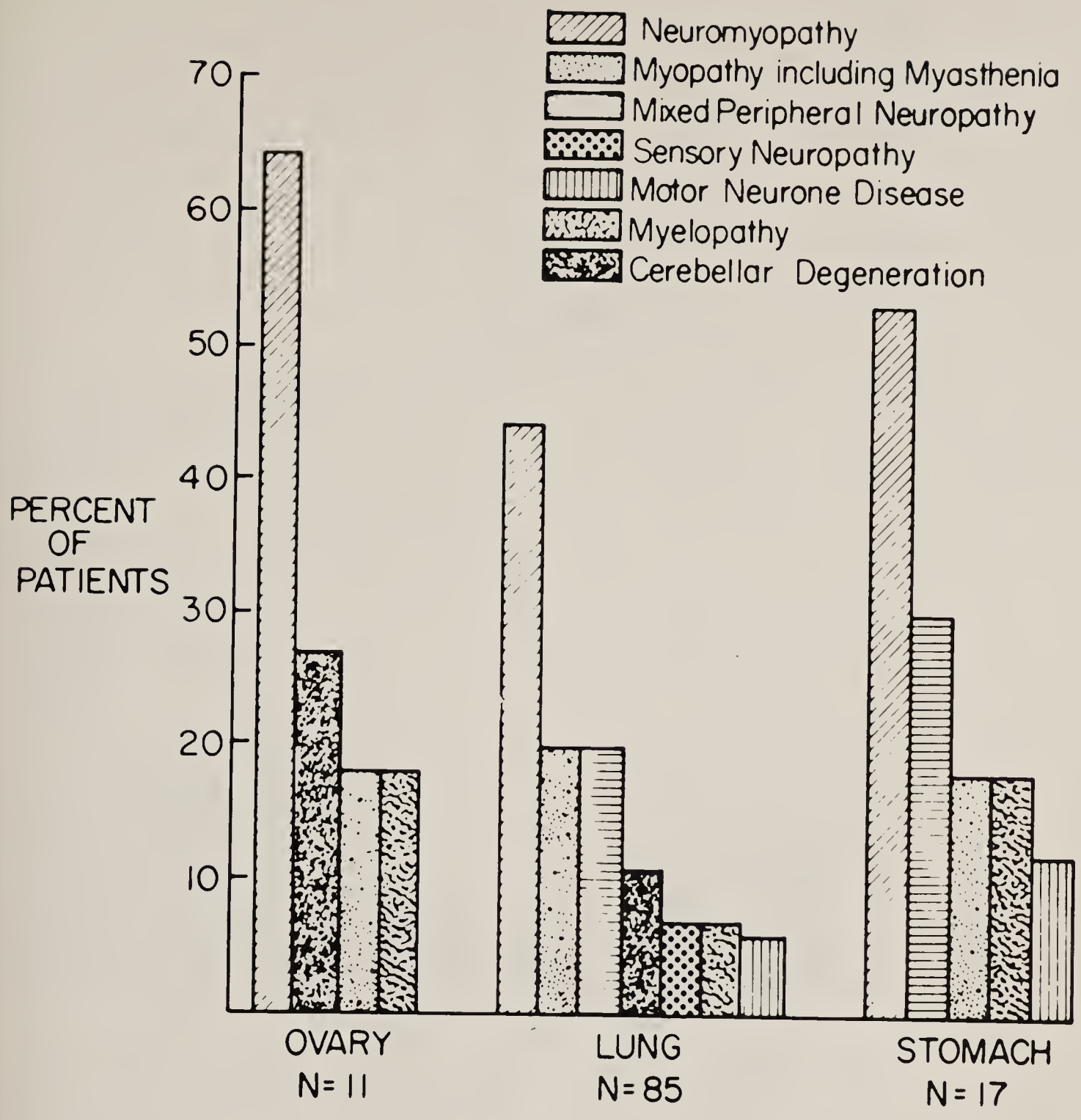

Fig. 2—Incidence of various neurologic syndromes in carcinoma of the ovary, lung, and stomach (modified from Croft and Wilkinson[3]). *Note:* The total incidence in each tumor group exceeds 100% because patients with multiple neurologic diseases were counted more than once.

spinal cord lesions are rare.

In short the focal lesion may appear virtually anywhere in the central nervous system from the cerebrum to the spinal cord. It is important to realize that the focal nature of the process may be clinically obscure and that diffuse symptoms such as lethargy, stupor and dementia may actually be the clinical summation of multiple small focal lesions. Headaches and seizures, although seen in PML, are uncommon and are more likely due to the underlying disease. Lastly, although focal lesions in the background of a systemic debilitating disease are the hallmarks of PML, it should be stressed that PML is rare, and focal parenchymal and meningeal metastases

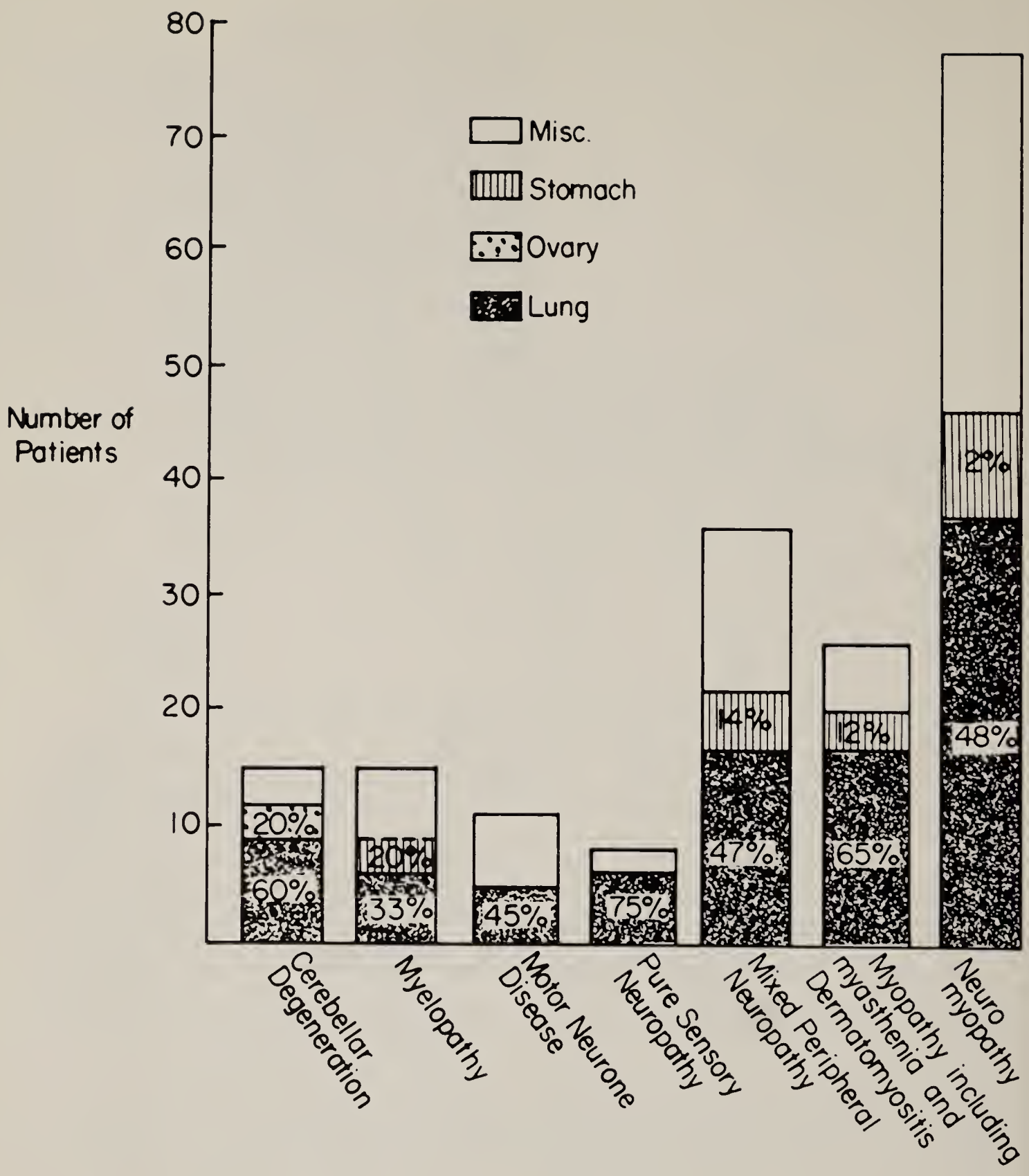

Fig. 3—Site of primary carcinoma in 162 patients with different types of neurologic deficits (modified from Croft and Wilkinson[3]).

are in comparison common.

An understanding of the spectrum of associated diseases is critical if one is to diagnose PML. The overwhelming majority of patients have had lymphoproliferative, myeloproliferative or non-neoplastic processes involving lymphoid tissue. Table II is a composite of two reports[5,6] and shows that those diseases constitute 82 percent of the associated disease states. Lymphoproliferative diseases alone accounted for over half (56 percent). The miscellaneous group is somewhat puzzling insofar as these patients lack a common denominator other than their chronic debilitating disease. Debilitation alone however would not explain the five reported cases in which there was no relevant disease whatsoever. These sporadic cases of PML occurred in

TABLE II

DISEASES ASSOCIATED WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
(112 PATIENTS)

	ZURHEIN	RICHARDSON	TOTAL
LYMPHOPROLIFERATIVE DISEASES			
Chronic lymphocytic leukemia	5	15	20
Hodgkin's disease	6	19	25
Lymphosarcoma	6	8	14
Plasmacytoma	0	2	2
Reticulum cell sarcoma	1	1	2
Mycosis fungoides			1
			64
MYELOPROLIFERATIVE DISEASES			
Chronic myelocytic leukemia	2	6	8
Acute myelocytic leukemia	0	1	1
Polycythemia vera	0	3	3
			12
NON-NEOPLASTIC GRANULOMATOUS DISEASES			
Sarcoidosis	1	5	6
Tuberculosis	2	6	8
Pulmonary anthrasilicosis	0	1	1
Whipple's disease	0	1	1
Primary hypersplenism	0	1	1
			17
MISCELLANEOUS DISEASES			
Carcinomatosis	0	3	3
Lupus	1	3	4
Chronic asthma	1	1	2
Cirrhosis of the liver	0	1	1
Hepatosplenomagaly	0	1	1
Diabetes mellitus with dissecting aneurysm	0	1	1
Unknown	0	2	2
No relevant disease	1	4	5
			19

previously healthy people[7] and four of these cases had pathologic documentation of PML.

The age of onset of the disease has ranged from 28[8] to 84[9] years of age. The average life expectancy after the onset of neurologic symptoms ranged from several days[10] to five years, the latter in a patient who exhibited a highly unusual course of remission and exacerbation.[11] Most commonly the disease progresses to death in two to twelve months. There is a sex predilection with males predominating 3:2 over females. To date PML has not preceded the onset of the systemic disease.

The diagnostic workup is disappointingly unrewarding. Nonspecific slowing on the electroencephalogram is not uncommon and there has been one unconfirmed report of a positive brain scan.[12] Investigation by pneumoencephalography and arteriography are invariably normal. Examination of the cerebrospinal fluid (CSF) occasionally yields moderate pleocytosis and modest elevations of the spinal fluid protein.

Little has been added to the pathology of PML since the initial descriptions from Richardson's department in 1958, summarized in his review in 1961.[13] The characteristic findings are:

1. There is total disappearance of myelin sheaths with relative preservation of axis cylinders.
2. There are often gigantic reactive astrocytes with bizzare nuclei and occasional unequivocal mitotic figures in many cases.
3. There is complete absence of any

acute or chronic perivascular inflammatory infiltrates.

4. The oligodendroglia display nuclear enlargements, and frequent eosinophilic intranuclear inclusions are seen.

Although the astrocytic changes were more dramatic and impressive to some, it is the changes in the oligodendroglia which Richardson carefully described that are the earliest and most constant lesion of the disease.

Richardson credits Waksman with the original hypothesis of a viral etiology.[14] This was confirmed in 1965 when ZuRhein and Chou were able to demonstrate with electron microscopy viral-like particles in the nucleii and cytoplasm of the oligodendroglial cells from early lesions of PML.[15,16] Since then, ZuRhein has reviewed eight of her own cases and 21 cases of other investigators, all with electron microscopic evidence of viral particles.[4] Viral particles have not been demonstrated in the bizzare astrocytes.

The viral particles have an icosahedral-shaped capsid, no envelope and tend to form crystalline intra-cellular masses—all characteristics suggestive of the group of viruses known as the papovaviruses. These small DNA viruses are a recent addition to the taxonomy of viruses. The papovavirus group is composed of four viruses: (1) the SV 40 virus, a latent virus isolated from monkey kidney which was later found to cause tumors in hamsters and other small laboratory animals; (2) the polyoma virus, a virus of mice which, as its name implies, is capable of causing many different types of tumors, including ependymomas in hamsters; (3) the K virus of rabbits and mice which causes pneumonitis and; (4) the papilloma virus, the only known human pathogen in the group, the cause of the common wart.

The characterization of the papovavirus-like particles seen in PML is incomplete at the time of this writing. One major roadblock has recently been removed with the report of the successful cultivation of papova-like virions in primary cultures of human fetal glial cells.[17] These authors suggested that initial studies on cell susceptibility and antigenicity indicated a new papovavirus. Another group[18] however collected evidence that the virus of PML may be related to SV 40. They reported the isolation of a papovavirus from the brains of two patients and demonstrated neutralization of the isolates by anti- SV 40 sera prepared in rabbits. These authors also were able to demonstrate a rising antibody titre for the first time in the serum of one of their patients. This represents an important link between PML and its pathogenesis by a papovavirus. Important as this may be, conclusive proof is still lacking, since there has been no successful transmission of the disease and since serologic diagnosis has been made in only one case. To confuse the issue slightly, some patients with PML have no anti SV 40 antibody levels detectable. The significance of this finding is difficult to assess since many of these patients are immunosuppressed and have diseases which affect the immunologic system. Furthermore there have been very few cases where the diagnosis has been made early enough to allow for a thorough immunologic evaluation. The presence of elevated serum antibody levels to an agent as unusual as SV 40 might lead one to attach causal significance to that finding. However there have been reports of significant anti-SV 40 titres in patients with no known exposure to SV 40.[19] In short, the possibility of viral presence as a result of secondary invasion or as an innocent bystander has not been completely excluded.

The implication of a papovavirus in an etiological role in PML is an exciting concept with far-reaching ramifications both for neurology and for virology. For neurology it represents the first link in the human animal of a virus capable of causing a selective demyelinating lesion by virtue of its specific affinity for those cells of the CNS whose function it is to maintain myelin—the oligodendroglia. For virology the implications are sobering when one contemplates the vast numbers of people who received the early

parenteral polio vaccines and the more recent adenovirus vaccines which were contaminated with SV 40 virus.

In summary, 15 years ago PML was an unknown disease; 10 years ago it was a rare neurologic disease of obscure origin; 5 years ago it was linked to a virus. Today it represents a controversial disease which raises provocative questions of our concepts of demyelination and of activation of latent viruses.

DIFFUSE POLIOENCEPHALOPATHY

Diffuse polioencephalopathy is a waste-basket term for a group of diseases which are clinically diverse but which share some pathological similarities. The term was first applied by Brain in 1965 and was meant in its most broad and simple sense—diffuse disease of the grey matter. The term is purposefully non-committal as to the etiological nature of the process. Inflammatory? Toxic? Degenerative? Its chief usefulness is to differentiate this disease from processes involving white matter in the CNS and from processes involving the peripheral end of the nervous system.

The title of this section should be more appropriately "the diffuse polioencephalopathies" or "the polioencephalomyelopathies," for a variety of clinical presentations is possible with dysfunction at a single level or at multiple levels of the neuraxis, from the cerebrum to the spinal cord. In 1934 Greenfield reported two cases under the title of subacute spinocerebellar degeneration occurring in two patients, one of whom had a tumor removed from her breast 10 months earlier and the other of whom had a bronchogenic carcinoma.[20] Greenfield made no suggestion at that time of a causal relationship. That remained for Brouwer and Biemond to do in 1938.[21] Greenfield's patients presented with dementia, weakness and pain in the legs as well as cerebellar symptoms of ataxia and dysarthria. Pathologically there were cerebellar purkinje cell loss and degeneration of the cerebellar-brain stem-spinal cord connections. However there was also pyramidal tract degeneration and no pathological explanation of the dementia. Further, there were intense perivascular infiltrates in the areas of the degenerating tracts. Brain, Daniel, and Greenfield reported three new cases and reviewed eight others under the title of subacute cortical cerebellar degeneration in 1951.[22] All of their cases had appropriate cerebellar symptoms with pathological correlation but they too had cerebral symptoms of dementia and memory loss for which there were no pathological findings. Furthermore one patient had pyramidal tract degeneration. Brain and Henson in 1958 reported three cases under the name of "mixed form of cerebellar degeneration" who in addition to clinical and pathological cerebellar findings had degeneration of the motor neurons of the brain stem and of the spinal cord, pyramidal tract degeneration and degeneration of the posterior columns, which had not been previously reported to be involved in this type of cerebellar degeneration.[23] The presence of a significant inflammatory response led these authors to suggest encephalomyelitis as a more accurate term for this condition. Similar cases of mixed findings had been reported by Henson's group four years earlier.[24]

In 1965 Henson, Hoffman, and Urich reported five new cases and reviewed five other cases under the title of encephalomyelitis.[25] With this paper they attempted to extend their concept of an inflammatory process. They felt these patients had an inflammatory disease purely involving neurones. The pathology in these patients showed limbic lesions with inflammatory infiltrates, lesions in the motor nuclei of the brain stem characterized by degeneration and lymphocytic infiltrates, loss of anterior horn cells in the spinal cord, and finally destruction of posterior root ganglia with Wallerian degeneration of both posterior columns and peripheral nerve. The authors point out that 9 of 10 patients had lesions at more than one site. Corsallis and his associates reported three cases which they present as a pure limbic encephalitis—[26] all with memory loss and

limbic neuronal degeneration and loss with inflammatory perivascular cuffing. However one patient also had wasting and weakness of the extremities and dysmetria, neither of which was explained pathologically. Another patient's memory loss was possibly on the basis of dementia which apparently began significantly earlier. Furthermore in all cases the inflammatory cuffing was present in other areas of the brain distant from the limbic neuronal loss, most notably in the brain stem. The description by Denny-Brown[27] of a pure sensory neuropathy associated with cancer completes our review of the spectrum of this disease which the literature has classified under the title of diffuse polioencephalopathy. The particular neurones involved in this disease are those of the dorsal root ganglion, and lymphocytic perivascular cuffing is present. However, as is true of the cases discussed above, this disease is not selectively limited to the dorsal root ganglion, and inflammatory infiltrates can be seen in other areas of the brain.

In summary, despite the earnest efforts of some excellent neurological investigators, we are nonetheless left with a group of diseases whose only common ground is their involvement in neurones. The fit between the clinical symptomatology and the pathology is imperfect, both with pathologically unverified symptoms and with asymptomatic pathological findings. Whether we are dealing with multiple manifestations of a single disease or several different diseases is impossible to determine. Under the circumstances it would appear to be the better part of judgment to refrain from forcing every case into an uneasy pigeonhole solely for the purposes of classification. The practicing physician should approach these diseases simply as diseases of unknown etiology which diffusely affect the neurones of the nervous system and which in any given patient may *predominantly* present clinically in one of three ways: (1) subacute cortical cerebellar degeneration (2) encephalomyelitis, or (3) the pure sensory neuropathy of Denny-Brown.

When we group these patients according to the predominant manifestation of their disease, several clinically useful facts emerge. It is striking that a cerebellar presentation places the patient in a different group when we analyze for the associated tumor. Figure 4 represents a composite of three different series of patients with subacute cerebellar degeneration in association with a tumor.[22,24,28] Figure 5 is a similar composite for encephalomyelitis.[25,26] Carcinoma of the lung accounts for almost 80 percent of the tumors associated with encephalomyelitis, with no other tumor even close. However carcinoma of the ovary (31 percent) is second after carcinoma of the lung (46 percent) as the associated tumor in patients with subacute cerebellar degeneration. More emphatically we can say (Figure 3) that in no other neurological syndrome does any tumor come this close to equaling lung cancer in incidence.

Another remarkable aspect of the association of cancer of the ovary with subacute cerebellar degeneration is the frequency with which the cerebellar symptoms precede the discovery of the tumor. In the series of Brain and Wilkinson,[28] 12 of 19 patients manifested cerebellar symptoms fron one month to eight years prior to the discovery of the tumor. Ten of the 12 however developed symptoms within two years of the discovery of the tumor. Whether this is due to the peculiar ability of small carcinomas of the ovary to cause this syndrome or to the well known difficulties involved in the early diagnosis of cancer of the ovary is unknown.

While it is obvious that the statistical and temporal associations discussed above are open to question because of the paucity of the experience in the literature, these observations must be accepted until better data prove them inadequate. This is especially true in the case of subacute cerebellar degeneration in which the appearance of the neurological disease may be the early clue to an underlying malignancy which is commonly difficult to diagnose. Sensory neurinopathy, which presents primarily as a peripheral neuropathy, will be dis-

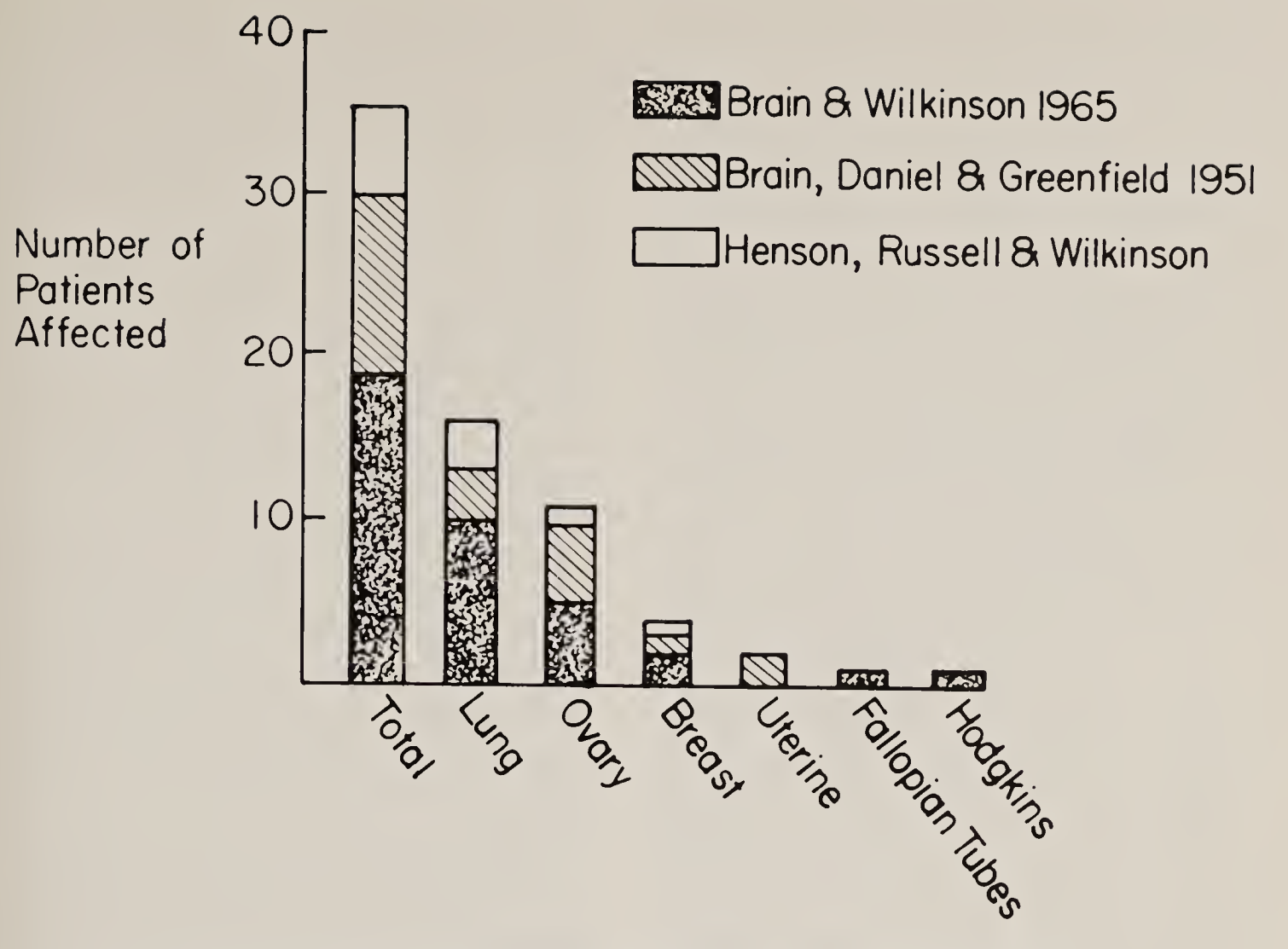

Fig. 4—Site of primary carcinoma in 35 patients with subacute cerebellar degeneration.

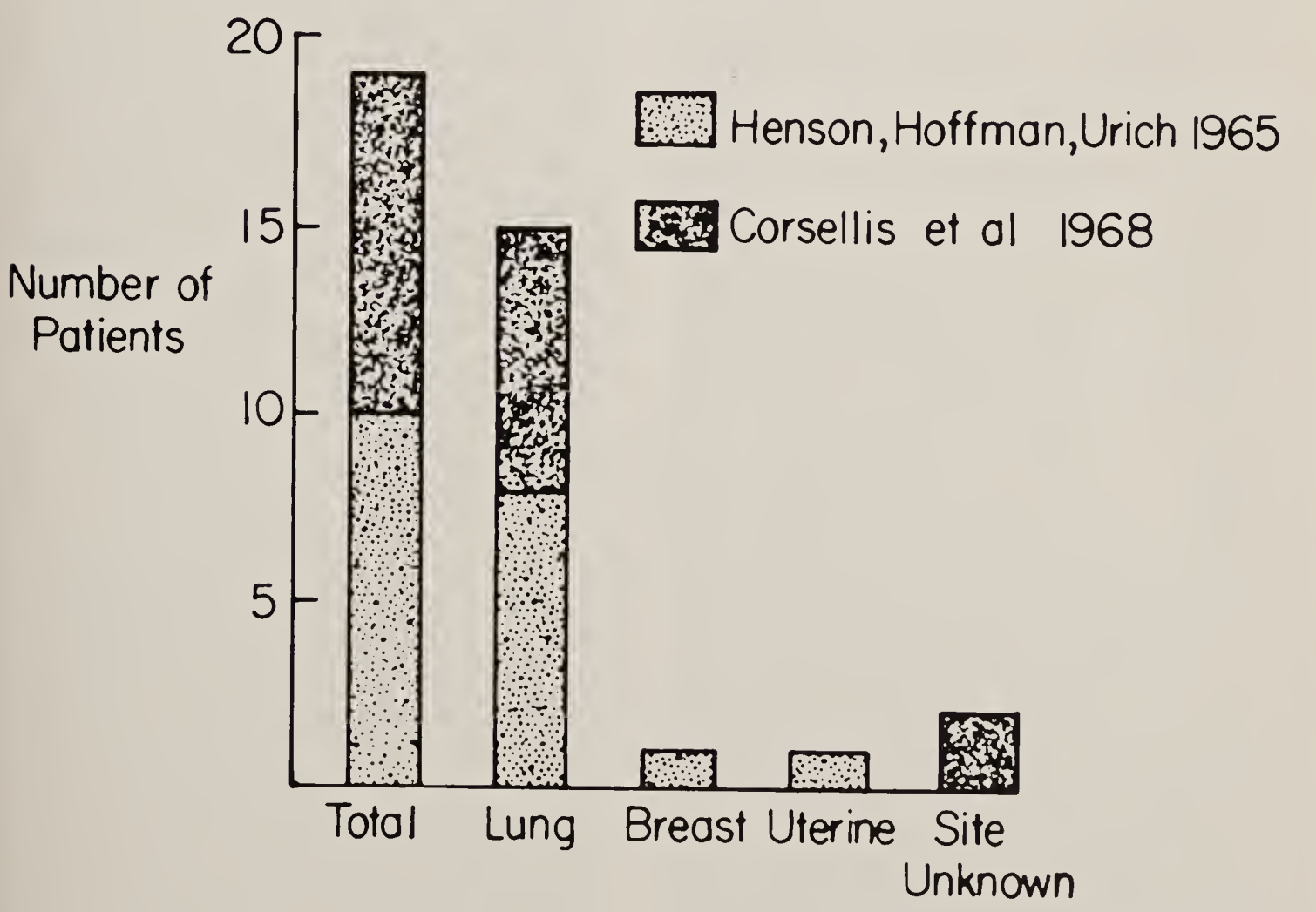

Fig. 5—Site of primary carcinoma in 19 patients with encephalomyelitis.

cussed in conjunction with the other neuropathies.

Progressive Necrotic Myelopathy

Progressive necrotic myelopathy (PNM) is a devastating insult to the spinal cord in which the patient experiences the painless onset of an acute or subacute ascending segmental sensorimotor deficit which progresses to dense paraplegia, anesthesia, and incontinence. The spinal cord displays roughly symmetrical patchy necrosis involving both grey and white matter equally. There is no localization of the necrosis to any particular fiber tracts or histologic cell type. The thoracic level of the spinal cord may be most severely affected. An important pathological feature is the involvement of the blood vessels in the necrotic process, with a curious eosinophilia in the vessel walls. The vascular alterations are not seen in areas outside of the areas of necrosis. Reactive gliosis may be more or less prominent depending on the age of the lesion. The complete absence of inflammatory infiltrates makes myelopathy, rather than myelitis, the term most suitable for this condition.

The disease is uncommon with only 80 or so cases reported. It affects men and women equally and spans ages from the first to the eighth decade with no race predilection. The course is one of rapid onset of weakness or heaviness of one or both lower extremities, sometimes associated with sensory dysesthesias or paresthesias. Over the course of hours to days there is relentless progression of the motor and sensory deficits most commonly resulting in a flaccid paralysis invariably associated with sphincter dysfunction. Some patients go on to spastic paraparesis, while others do not. In most there is ascending progression to commonly involve the trunk, frequently involve the upper extremity and rarely involve the bulbar area. The patient dies in weeks to months, usually from intercurrent infection.

The etiology of the disease remains obscure but heavy metal toxicity, tetanus antitoxin, gout, hypertension, radiation therapy, and trauma have all been mentioned in the literature. The relationship to cancer has also been noted and Mancall and Rosales tabulated nine cases from the literature and added two of their own.[29] The age of onset in the cancer group ranged from 17 to 74 years and in general reflected the tumor type rather than any age predilection for the neurological condition. The neurologic condition in no case preceded the discovery of the tumor and, once begun, the course of the myelopathy was more fulminant than when not associated with malignancy. Of the 11 patients the maximum survival was two months. Five of the 11 patients had carcinoma of the lung and the remaining six were represented by carcinoma of the prostate, stomach, thyroid, breast, squamous cell carcinoma of the skin, and giant cell sarcoma of the leg.

The diagnosis of progressive necrotic myelopathy should be made only after more common and more treatable causes have been excluded. Any patient presenting with the sudden onset of a disease causing a motor-sensory level must be evaluated for spinal cord compression by tumor, epidural abscess, or herniated disc. A myelogram with a Queckenstedt test and with fluid taken for appropriate bacterial, chemical, and cytological studies should be done rapidly. With a space-occupying lesion ruled out, one would then consider vascular infarction, and acute demyelinative diseases such as transverse myelitis. The patient's progressively ascending course over the next few days would also provoke a diagnosis of Guillain-Barré syndrome. Some clinical distinction can be made however on the grounds that Guillain-Barré tends to present mostly with a motor deficit and may spare sphincters, whereas PNM virtually invariably involves sphincters and sensory function as well as motor function. The spinal fluid in progressive necrotic myelopathy is nondiagnostic but is abnormal with elevated protein and a mild cellular response. By and large the diagnosis must be made on clinical grounds and frequently one must allow

the patient's subsequent course to declare itself. Transverse myelitis, vascular infarction, and Guillan-Barré all tend to stabilize or improve, whereas PMN uniformily deteriorates.

Peripheral Neuropathy

The most common remote site of carcinomatous involvement is at the peripheral level of the nervous system. Pure sensory neuropathy, mixed peripheral neuropathy and neuromyopathy, as a group, comprised 121 of a total 188 neurologic deficits in the 162 patients represented in Figure 3. The largest group has been termed "neuromyopathy" or neuromuscular disorder because of the difficulty, especially in mild cases, of determining whether the defect is primarily in the peripheral nerve or in the muscle. These patients present with bilateral symmetrical proximal wasting and weakness with a dimunition or loss of deep tendon reflexes. Because these latter patients present clinically as a myopathy we have chosen to discuss this disease (see Table I) with the other myopathies.

Under the present topic of discussion we would include two diseases: (1) sensory neuronopathy and (2) mixed sensorimotor polyneuropathy.

Sensory Neuronopathy: The ability of malignancy to remotely affect the dorsal root ganglion, producing a pansensory deficit was beautifully described by Denny-Brown in 1948.[27] It is a rare disorder and alternatively has been called carcinomatous sensory neuronopathy and ganglioradiculitis.

The disease presents with a subacute onset of sensory symptoms which gradually worsen over several months, after which the patient usually stabilizes for a significant period of time. Paresthesias of both upper and lower extremities are the typical presenting complaint. The patient displays a sensory ataxia and may show pseudoathetoid motions or irregular involuntary straying movements of the fingers. The sensory ataxia frequently appears to be disproportionately more severe than the underlying proprioceptive deficit. Symptoms of distal burning pains which are a classic sign of peripheral neuropathy are not invariably present in this condition.

Pathologically there is destruction of neurones in the posterior root ganglion with bidirectional Wallerian degeneration of the posterior columns and peripheral nerves. Also seen are scattered inflammatory lesions in the brain and spinal cord, a finding which has led some authors to classify this disease as one manifestation of encephalomyelitis rather than as a peripheral neuropathy. The presence of some inflammatory lymphocytic perivenular infiltrates in the dorsal roots has led other authors to introduce the term ganglioradiculitis. Careful nerve conduction studies can establish the diagnosis by demonstrating a prolonged nerve conduction time for sensory fibers and a normal conduction time for motor fibers. Electromyography (EMG) should be normal since there is no significant involvement of the motor neurone or the muscle. CSF analysis frequently reveals elevated protein levels which merely confirms the clinical impression of a peripheral neuropathy but is otherwise nonlocalizing.

The etiology of this condition is obscure. The theory of immunologically mediated tissue injury has received some support by the demonstration of serum complement-fixing antibodies and fluorescent antibodies against antigens prepared from guinea pig brain.[30,31] This finding has not been verified. The possibility of a viral etiology has been mentioned[32] frequently but to date there are no hard data which implicate a virus. The associated tumor is overwhelmingly of the lung, and a thorough cancer search is indicated in any patient presenting with a pure sensory neuronopathy.

Mixed Sensorimotor Polyneuropathy: The clinical presentation of distal weakness and wasting, sensory loss or dysesthesias, and associated diminution of deep tendon reflexes constitute the classical clinical entity of perpheral neuropathy resulting from a variety of causes. The presentation of peripheral neuropathy of underlying malignancy possesses

no identifying markers which allow clinical differentation from the other myriad causes of peripheral neuropathy. Predomination of either motor or sensory symptoms may occur, the latter of which may be difficult to distinguish from pure sensory neuronopathy (*vide supra*). Croft and associates[33] have evaluated 33 patients with sensorimotor neuropathy and divided them into three groups:

1. Mild and often terminal peripheral neuropathy in the course of known malignant disease,
2. Subacute or acute *severe* peripheral neuropathy, often preceeding the discovery of the tumor,
3. Severe peripheral neuropathy, somewhat similar to group (2), but with a more fluctuant course of symptoms.

All three groups were represented in the 10 patients who were examined pathologically, and similar findings of axonal damage, demyelinization, and Schwann cell proliferation were demonstrated in all cases. Examination of teased preparations of individual nerve fibers, designed to determine whether primary axonal damage or primary demyelination is at the root of the process, has revealed segmental demyelination with relative preservation of axons in the two cases studied. While this is inconclusive it suggests the disease is initiated by a demyelinating or Schwann cell defect.

The clinical grouping of these patients is not confirmed by pathologic distinctions. Yet it is clinically useful for two reasons. First, the patients with mild insidiously developing deficits are rarely incapacitated by their neurologic disease, whereas this is common in patients with a more acute onset. Secondly, in none of 10 cases in the group with mild symptoms, did the neurologic symptoms precede the discovery of the malignancy, whereas 10 out of 23 patients with more severe disease had no evidence of malignancy at the time of onset of neurologic disease but were discovered to have a malignancy from four months to six years later. Therefore we feel it a clinically useful rule of thumb that the more rapid the onset and the more severe the evolving deficit, the more suspicious one should be of the presence of an underlying malignancy.

Laboratory examination of the CSF and electrodiagnostic tests reveal findings consistent with a peripheral neuropathy but do not help greatly to support a carcinomatous etiology. Spinal fluid protein is commonly elevated. Levels of 80 to 150 mg/100 ml are typical but occasional levels of 300 to 360 mg/100 ml are seen. Nerve conduction is usually normal or moderately depressed (20 to 30 m/sec). Severe decreases in conduction velocity have been noted, however, which is not surprising in light of the pathology of segmental demyelination in some cases. The EMG shows evidence of denervation in some patients. In short, the laboratory merely confirms our clinical diagnosis of a peripheral neuropathy. The proof of a carcinomatous etiology rests upon the discovery of the tumor. The most commonly associated tumor is lung cancer.

THE MYOPATHIES

Muscle fatigue and weakness are perhaps the most common complaints of patients with cancer, and frequently the most frustrating for the physician. Abnormalities of endocrine-electrolyte origin should always be considered, as they are potentially reversible. Cushing's syndrome, hypercalcemia and inappropriate antidiuretic hormone (ADH) are discussed thoroughly in another section of this symposium. Cachexia alone, and for reasons poorly understood, may be the sole explanation of a patient's weakness. Neurologically, diffuse, symmetrical bilateral weakness may be the presentation of either neurogenic or myopathic disease states. In a patient with a known malignancy under treatment, the possibility of a drug-induced neuropathy (vincristine) or myopathy (steroid) always exists. The neurogenic causes of weakness have been discussed in the preceding section. The myopathic causes will be discussed here.

Primary involvement of muscle tissue may be in the form of polymyositis, myasthenia gravis, the myasthenic syndrome of Eaton-Lambert, dermatomyo-

sitis or a less specific entity which is best described simply as carcinomatous neuromyopathy.

Myasthenia and the Eaton-Lambert Syndrome: Myasthenis gravis is a disease of the neuromuscular junction, involving the voluntary striated musculature. Symptomatology is one of weakness which is aggravated dramatically by exertion and is reversed by rest and by specific drugs. The muscle weakness may present as ocular myasthenia with diplopia and ptosis, as bulbar myasthenia with dysarthria, dysphagia and difficulty in mastication, or as skeletal myasthenia with generalized weakness or with selective weakness limited to the face, neck, or one or two extremities. Ocular manifestations are a common and perhaps best known chief complaint but usually other areas of involvement can be found on examination. Patients with a more generalized form of this disease may be so severely stressed as to develop the myasthenic crisis which is characterized essentially by hypoventilation and respiratory insufficiency. Females outnumber males 3:2 and have a peak incidence in the third decade, as compared to the sixth decade for males.

In the years after the discovery of acetylocholine as the neuromuscular transmitter, it was discovered that physostigmine improved patients with myasthenia gravis and it became accepted that the defect primarily lay in insufficient amounts of cholinergic activity at the neuromuscular junction. The *Tensilon test*, involving the intravenous administration of this anticholinesterase with concomitant improvement in the patient, became widely accepted as a useful diagnostic tool. Electromyographic findings in myasthenia gravis show a decrease in the action potential with repetitive stimulation. A normal muscle would not show this electrical evidence of fatigue under similar conditions.

Several lines of evidence implicate the immunological system in the etiology of myasthenia gravis. First it has been associated with several disease states which fall in the category of autoimmune disease—thyroid disease,[34] rheumatoid arthritis, systemic lupus erythematosus, scleroderma,[35] pemphigus,[35] and polymyositis.[36] Secondly, various abnormal antibodies and autoantibodies have been found in the sera of patients with myasthenia, *e.g.*, antinuclear antibodies[34] and antiskeletal muscle antibodies.[38] Thirdly, a role for cell-mediated immunity is suggested by the work of Armstrong[39] and others that lymphocytes from patients with myasthenia gravis are sensitized to muscle antigens. Fourthly, abnormalities of the thymus, an organ whose importance in the immunologic system has recently come into greater focus, have long been noted to be associated with myasthenia gravis. Lastly, therapeutic measures aimed at suppressing the immunologic system, such as antilymphocyte serum, immunosuppressive drugs and thymectomy, have met with some success.

It is not surprising therefore to find that thymic tumors are encountered in myasthenia. Rubin and his coauthors reviewed several large series of thymic tumors and the number of patients with associated clinical myasthenia. The incidence in the different series varied from 7 percent to 48 percent. From the opposite standpoint looking at thymuses from patients with myasthenia 65 to 70 percent are abnormal, varying from hyperplastic persistent germinal centers to actual thymomas. Opinions vary on what constitutes a thymic tumor, the subtypes of tumors and even whether a given tumor is malignant, since mitoses and distant metastases are rare. Using strict criteria, the incidence of true thymomas in myasthenia gravis probably lies around 10 percent. Thymic tumors should be radiographically sought in any patient with myasthenia, and, conversely, surgeons should be wary of the sudden onset of preoperative and postoperative myasthenia gravis in any patient being considered for thymoma resection, especially since such patients may be supersensitive to curarizing agents.

The therapeutic approach to a patient with myasthenia is complicated and con-

troversial. There is good agreement that resection is indicated in a patient with a radiographically demonstrable thymoma. However whether or not a patient with myasthenia should be subjected to surgery to remove questionably abnormal thymic remnants is a far more controversial question. Many of these patients have had a far milder course after resection, requiring little or no medicine. Others however remain unchanged, having gained nothing from the risk of surgery. A more detailed discussion is beyond the scope of this article and is adequately covered elsewhere.[40,41]

Eaton-Lambert Syndrome: The "myasthenic syndrome," now referred to as the Eaton-Lambert syndrome takes its name from the symptoms of weakness and fatigability which are common to this disease and to myasthenia gravis. Several authors suspected on clinical grounds that the two diseases were not identical.[42,24] This was confirmed several years later by the Mayo Clinic group,[43,44] when they demonstrated the features of the neuromuscular defect. Table III summarizes the clinical differences in the two diseases. The diagnosis should be suspected by the clinical presentation. The EMG will clearly confirm or refute the diagnosis. Figure 6 is a diagram of the response of a typical patient when asked to grip a bulb with maximum strength. In the normal patient there is no delay from time 0 until maximum strength is reached. There is a slight sagging of strength afterwards. With successive grips there is again no delay and also equal strength (height) is achieved. In Eaton-Lambert syndrome there is a definite delay in the achievement of maximum strength, and with successive grips not only does the delay persist but fatigue develops. This is clearly in contrast to myasthenia gravis where there is fatigue but no delay in achieving maximum strength. An even more dramatic demonstration is shown in Figure 7. Here each spike represents an action potential recorded from the hypothenar eminence after supramaximal stimulation of the ulnar nerve. The action potentials in the normal are all of equal height. In Eaton-Lambert the initial spikes are small and then gradually, with repetitive stimulation, increase to attain a normal height. Myasthenia gravis however starts with a normal height and then rapidly fades to subnormal levels.

The pathophysiology of these EMG findings was clarified by *in vitro* studies by Lambert.[45] Intracellular recordings of miniature endplate potentials were done in intercostal muscle biopsies from normal, myasthenic and Eaton-Lambert patients. Figure 8 compares the pattern and height of depolarization in the three conditions. Miniature endplate potentials represent the depolarization occurring at the endplate from spontaneous release of vesicles of acetylcholine. The number of

TABLE III

COMPARISON OF MYASTHENIA GRAVIS WITH EATON-LAMBERT SYNDROME

	MYASTHENIA GRAVIS	EATON-LAMBERT SYNDROME
Distribution of weakness	ocular bulbar and generalized	proximal skeletal muscles—esp. thigh
Reflexes	normal	weak to absent
Strength curve	maximum strength immediately, then diminishes	delayed development of maximum strength
Response to Tensilon	dramatic improvement	variable
Sensitivity to Curare	marked	marked
Tumor association	thymoma	oat cell carcinoma
Other symptoms	absent	dryness of mouth, paresthesias, muscle pain, impotence

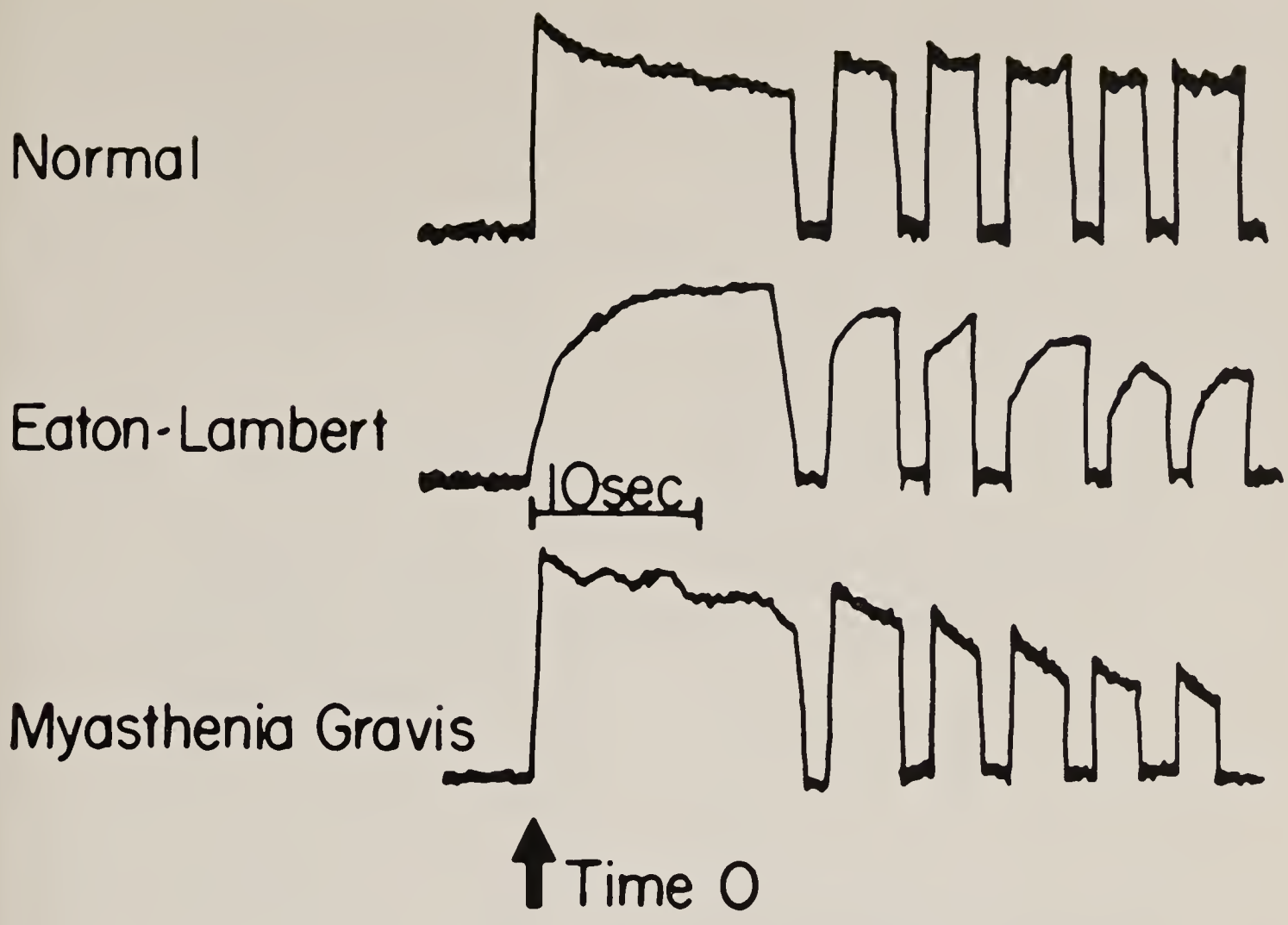

Fig. 6—Tracing of strength development upon squeezing a bulb, in patients with myasthenia gravis and Eaton-Lambert syndrome (modified from Lambert and Rooke[46]).

spikes reflects the number of acetylcholine packets released, whereas the amplitude of the spike is related to the amount of acetylcholine in the packet. In the normal we see the spikes are of roughly uniform height and at a "normal frequency." The decreased height of the spikes in muscle from patients with myasthenia would suggest that myasthenia gravis is a disease of insufficient acetylcholine per packet, whereas Eaton-Lambert is a disease of insufficient numbers of packets, each packet however containing a normal amount of acetylcholine. Therefore repetitive ulnar nerve stimulation or prolonged voluntary grip causes more and more packets to be released and maximum strength, although delayed, is eventually reached.

From a clinical standpoint there are several important facts. Sixty to 70 percent of patients have an associated oat cell carcinoma of the lung. The syndrome has been reported at as young as twenty years of age. The disease may precede the tumor, and all patients should be followed closely as tumor suspects. No tumor may ever be found in 20 to 30 percent of patients.[40] Treatment is directed primarily toward the tumor, and remissions of the symptoms have been noted upon resection of the tumor. Reappearance of the neuromuscular symptoms may occur with recurrence of the tumor. Neostigmine and other anticholinesterases are of limited use, but guanidine has reportedly been of help.[47] Muscle pathology is conspicuous by its absence.

Polymyositis and Dermatomyositis: Polymyositis is a disease whose diagnosis is entertained in a patient who presents with painful or painless weakness and severe wasting predominantly affecting the proximal musculature in the absence of reflex changes or sensory deficit (un-

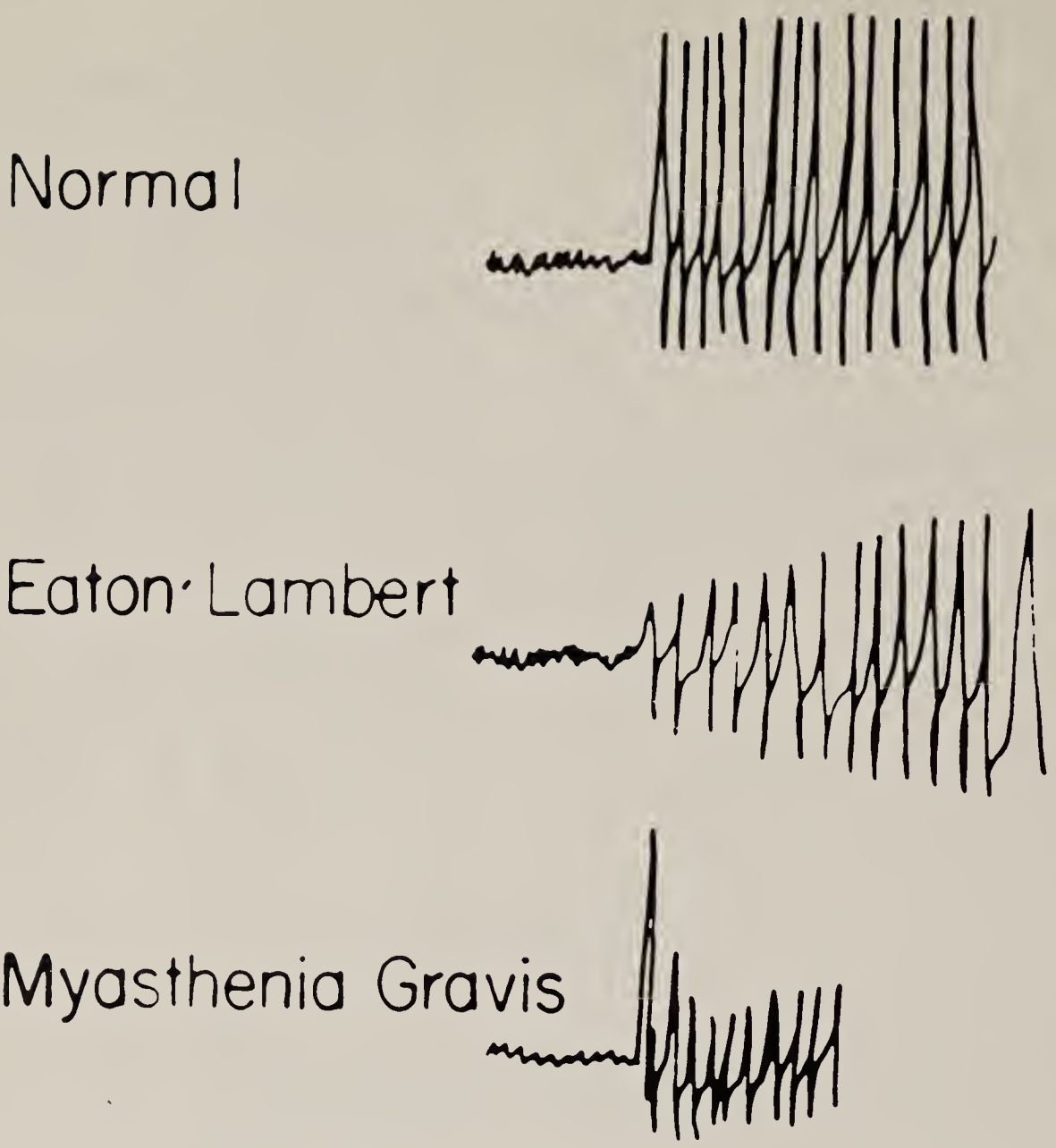

Fig. 7—Diagram of typical action potentials evoked by supramaximal stimulation of the ulnar nerve (modified from Lambert and Rooke[46]).

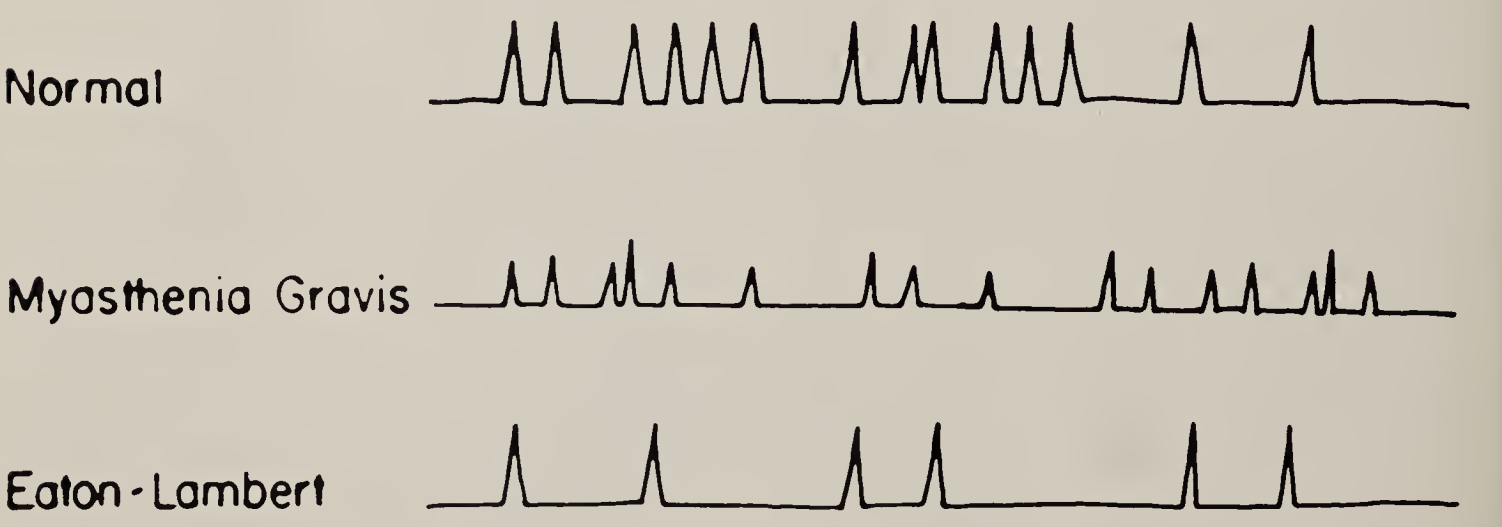

Fig. 8—Diagrammatic representation of miniature endplate potentials recorded in *in vitro* preparations from intercostal skeletal muscles (modified from Elmqvist and Lambert[45]).

less wasting is endstage). The course may be gradual in onset over months to years, or more rapid, leading to severe locomotor incapacity in mere weeks. The chronic form of the disease was frequently misdiagnosed as adult muscular dystrophy.

The disease may present with nonspecific systemic signs such as fever and weight loss in five percent of patients. The chronic form may have arthritic complaints. A good number of patients, perhaps 25 percent, present with polymyositis and a skin rash of an erythematous (heliotrope) and edematous appearance involving the malar and eyelid areas of the face, the upper chest, and, very commonly, the extensor surfaces of the joints. The skin lesions and muscle findings together constitute dermatomyositis. Occasionally the skin lesions may precede the muscle disease but concomitant appearance or the reverse sequence is most common. The name of the disease is taken from the frequent, although not universal, pathological finding of inflammatory cell infiltrates in the muscle.

Laboratory findings are quite helpful. Elevations of the sedimentation rate are present in 50 percent of patients. In a patient with the active disease, serum glutamic oxaloacetic transaminase (SGOT) and aldolase activities are always elevated. CPK is more variable. With effective treatment, serum enzyme activities fall. Electromyography provides good support in the diagnosis of polymyositis. The findings have been adequately discussed by Walton and Adams.[48]

The association of malignancy with myositis was first noted in the English literature by Bezecny in 1935[49] although it had earlier mention in the German literature. Many reports have appeared in the last 30 years.[48,50–53] Pearson has reviewed all cases reported up until 1964[54] and pointed out that (a) 15 to 20 percent have malignancy (b) all but two reported cases were over the age of 40 and (c) most had skin lesions and a florid course. This last point is emphasized by Rowland and Schotland[55] who, while admitting a possibly similar pathologic mechanism, argue to maintain polymyositis as a separate diagnostic entity from dermatomyositis, citing a higher mortality and higher incidence of cancer in patients with rash. Eaton however regards polymyositis as a noncutaneous form of dermatomyositis.[56] Rowland and Schotland[55] reviewed the literature and the experience at Columbia-Presbyterian Hospital and reported 487 patients with dermatomyositis, of whom 60 or 12.3 percent had a malignancy. Rowland[57] and Williams[53] reported that no tumor type prevailed. Ovary, breast, uterus, stomach and lung are perhaps most common but prostate, colon, gallbladder, kidney, thyroid, pancreas, esophagus, and parotid are also represented. Lymphoma and leukemia are perhaps least represented. Both Williams [53] and Arundel[58] state that in the great majority of cases the dermatomyositis precedes the tumor discovery.

The pathology of polymyositis is variable. One sees degeneration of muscle fibers with occasional necrosis and phagocytosis, interstitial fibrosis and most importantly chronic inflammatory lymphocytic and plasma cell infiltrates. Vasculitis is not a prominent finding. The pathology gives us very little etiological clue but the frequency of inflammation is consistent with the therapeutic success which has been achieved with steroids in recent years.

Therapy with steroids is currently the treatment of choice. Prednisone, 60 mg daily, is a reasonable starting dose but most importantly one must follow with serial enzyme determinations, for a drop in the enzyme activities appears to be an accurate reflection of the lessened activity of the disease. A drop in the enzyme levels can be anticipated two weeks after therapy is begun. Withdrawal of steroids may cause a sudden exacerbation of the disease. Therefore steroid withdrawal should be done only in conjunction with serial enzyme determinations. On reviewing several series[54, 59-61] one finds that 50 to 75 percent of patients will improve significantly. The failure group, including about 10 to 15 percent who go

on to die, are the group who also have malignancy.

The theories of etiology are interesting but unfortunately are not conclusively proven by objective data. An immunologic role is suggested by the intermediate position polymyositis occupies nosologically between autoimmune disease and cancer. Polymyositis is associated with Raynaud's disease in 30 percent of patients and with rheumatoid features in 50 percent of patients. The relationship to cancer has already been discussed. Recent evidence has further indicated an immunologic mechanism with the demonstration by Whitaker and Engel[62] of immunoglobulin and complement deposits in the walls of skeletal muscle blood vessels from patients with inflammatory myopathy. The deposits, demonstrated by immunofluorescence, were especially heavy in dermatomyositis of childhood.

Carcinomatous Neuromyopathy: This disease is the most difficult of the neuromuscular disorders to characterize. At the root of this difficulty lies the fact that it may not be a discrete pathological entity at all. The concept of this disease arose because there is a significant group of patients which remain after we have excluded those patients who have findings consistent with diagnoses of polymyositis, dermatomyositis, peripheral neuropathy, motorneurone disease, or drug-induced disease. Whether these patients represent a variant of one of the above diseases or whether they form one or more entirely separate diagnostic categories is unclear at this time.

G. Milton Shy has defined "neuromyopathy" as a "clinical syndrome of symmetrical proximal muscular weakness and wasting, associated with a decrease of the appropriate myotatic reflexes."[63] The absence of sensory findings and appropriate EMG and nerve conduction changes exclude peripheral neuropathy; the absence of consistent enzyme elevations, of skin rash, of consistent inflammatory infiltrates on muscle biopsy and of improvement on steroids makes polymyositis-dermatomyositis unlikely. Motor neurone disease is excluded on the basis of lack of fasciculations, characteristic clinical course, and of corroboratory EMG evidence of denervation.

Shy and Silverstein[63] studied a group of patients with this clinical syndrome in an attempt to further define the characteristics of this disease. Forty-two patients had both carcinoma and a neurologic deficit. Thirty-six cancer patients had disease of the motor unit. Twenty-seven of these fitted their definition of neuromyopathy and represented 64 percent of the 42 patients with both diseases. This compares with 77/162 (48 percent) from the series of Croft and Wilkinson (Figures 3 and 4), confirming the commonness of neuromyopathy as a remote effect of cancer on the nervous system.

The authors analyzed age and sex in those patients who had both cancer and a late onset of proximal myopathy as compared to patients with late-onset myopathy alone. Table IV shows that males over the age of 50 are at greatest risk.

TABLE IV

INCIDENCE OF MALIGNANCY IN 151 PATIENTS WITH PROXIMAL WASTING AND WEAKNESS ACCORDING TO AGE AND SEX*

	MALES		FEMALES	
	Total Number	% With Cancer	Total Number	% With Cancer
UNDER 50	35	3%	48	9%
OVER 50	25	60%	44	16%

*Modified from Shy and Silverstein[63]

The pathologic and laboratory data are not very homogeneous among this group of patients. Both cancer and non-cancer groups had evidence of inflammatory infiltrates on muscle biopsy. Enzyme activities and EMG data are difficult to interpret because the numbers were small and were not adequately controlled with an age-matched, non-cancer group.

The associated malignancy in this series occurred in 13 different sites, with lung cancer claiming five of the 27 patients.

In short the syndrome of carcinomatous neuromyopathy remains an unclear nosological entity. The diagnosis rests on the discovery of the tumor and should be sought for most vigorously in males over the age of 50.

SUMMARY

Involvement of the nervous system in association with cancer occurs in six percent of patients with cancer. Any level of the neuraxis may be affected, but the peripheral nervous system is the most common site of involvement. The most prevalent tumors responsible are of the lung, stomach, and ovary. Table V summarizes those syndromes which precede the symptoms of malignancy. With the exception of progressive multifocal leukoencephalopathy, which is probably a viral infection, the etiology of most of the syndromes and the role played by cancer is obscure. The diagnosis of remote involvement of the nervous system should be considered when metabolic and metastatic mechanisms have been excluded. Remission of the neurologic syndrome may follow effective tumor-directed therapy.

TABLE V

NEUROLOGIC SYNDROMES WHICH MAY PRECEDE THE DISCOVERY OF MALIGNANCY

DISEASE	TUMOR TYPE
Cerebellar degeneration	lung and ovary
Sensorimotor peripheral neuropathy	lung
Neuromyopathy (in the male)	lung
Myasthenia gravis	thymoma
Eaton-Lambert syndrome	oat cell ca of lung
Dermatomyositis	miscellaneous tumors

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REMOTE HEMATOLOGICAL MANIFESTATIONS OF MALIGNANT DISEASE

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INTRODUCTION

Hematological complications of malignant disease usually are due to the physical presence of the tumor. Anemia and thrombocytopenia secondary to marrow replacement are commonly seen, as is anemia secondary to bleeding, particularly from gastrointestinal tumors. In addition, there are hematological disorders in association with non-hematological malignancies which are not so clearly related to the tumor. The anemia of chronic diseases, erythrocytosis, pure red cell aplasia, thrombocytosis, non-myelophthisic thrombocytopenia, and leukemoid reactions are examples of such conditions. The pathophysiology of some of these disorders is being slowly revealed. The purpose of this article is to review the clinical presentation and pathophysiologic mechanisms of these syndromes.

THE ANEMIA OF CHRONIC DISORDERS

One of the most common abnormalities associated with cancer is anemia. Although all other causes of anemia may be present in patients with cancer, blood loss being especially common, many such patients will have no demonstrable cause for anemia. This condition, once called simple chronic anemia, has been referred to by Cartwright[1–3] as the anemia of chronic disorders. This anemia appears to be morphologically and functionally identical to that seen in chronic infections, rheumatoid arthritis, collagen diseases, fractures, severe tissue injuries and other disorders. Cartwright and Lee have defined the anemia of chronic disorders as "that anemia, usually mild in degree and not progressive in severity, which is characterized by decreased plasma iron, decreased total iron-binding capacity of the plasma, decreased saturation of transferrin with iron, decreased bone marrow sideroblasts, and normal or increased reticuloendothelial iron."[2] The appearance of this anemia may precede other signs of cancer. After its appearance, it tends to remain constant in degree, with a hematocrit typically in the 30-to-40 percent range. It also may present as a 10-to-15-percent fall in hematocrit from high to lower normal levels. There is a tendency for patients with widespread disease to have more severe anemia, but anemia can occur with localized lesions.

The hemoglobin and hematocrit may not adequately describe the erythron in this condition. Banerjee and Narang[4]

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demonstrated elevation of plasma volume in nearly 50 percent of patients with malignancy, some of whom had low hemoglobins and hematocrits but normal red cell masses. This spurious anemia can also occur in rheumatoid arthritis.[5] Conversely, in patients with anemia secondary to chronic infections, the severity of anemia may be masked by a decrease in the plasma volume proportionately greater than the decrease in red cell mass.[3]

The anemia is most frequently normocytic and normochromic. It may be hypochromic (MCHC 26 to 32 percent) and occasionally is hypochromic and microcytic (MCV 72 to 80). Cartwright and Lee have stated that in this disorder, hypochromia usually precedes microcytosis[2]—the opposite sequence from that seen in iron deficiency. The absolute reticulocyte count is usually within normal limits but may be increased to twice normal. Characteristic abnormalities in this disorder are listed in the Table.[2] The diagnosis may be made on the basis of the characteristic disturbances of serum iron and iron-binding capacity, the presence of bone marrow sideroblasts, and normal or increased reticuloendothelial iron. Coexistent iron deficiency may be diagnosed by the absence of reticuloendothelial iron. In cases of doubt, the administration of oral iron should restore the altered iron metabolism to that typical of the anemia of chronic disorders, if the two conditions coexist.

Three interrelated factors contribute to the development and maintenance of this anemia:

1. **Shortened Erythrocyte-Survival Time.**[3] Patients with this syndrome display decreased survival, both of their own cells and of compatible transfused cells; conversely, patients' cells survive normally in normal recipients. This implies that an extracorpuscular defect is responsible for the decreased longevity. Whether this defect is due to a circulating metabolite, to an immunological factor, or to an overavid reticulendothelial system is not known.

2. **Impaired Marrow Response to Anemia.** The decrease of red cell survival is usually slight, and this rate of hemolysis should be easily compensated for by normal marrow. However, the rate of red cell production measured by plasma and red cell iron turnover remains unchanged or increases insufficiently (only one to two times normal) to prevent the development of anemia.

Red cell production is normally accelerated by erythropoietin in response to tissue hypoxia (*vide infra*). Ward and his associates[6,7] have demonstrated that patients with this disorder may fail to increase serum erythropoietin levels or may increase it to a lesser degree than would be found in other anemias such as that due to iron lack. The anemia in both man[3] and animals[8] responds to cobalt, a known stimulator of erythropoietin release, and rats with anemia associated with inflammation respond appropriately to purified erythropoietin and to hypoxia.[9] This demonstrates that the ability to produce erythropoietin in response to physiological stimuli, and

VALUES FOR IRON, COPPER AND PORPHYRINS IN NORMAL SUBJECTS AND IN PATIENTS WITH THE ANAEMIA OF CHRONIC DISORDERS

Determination	Normal subjects	Chronic disease
Plasma iron (μg/100 ml)	100 (70–150)	30 (10–70)
Total iron-binding capacity (μg/100 ml)	350 (300–400)	200 (100–300)
Transferrin saturation (%)	30 (25–50)	15 (10–25)
Sideroblasts (%)	40 (30–50)	10 (5–20)
Reticuloendothelial iron	2+ (1 to 2 +)	3+ (2 to 6+)
Plasma copper (μg/100 ml)	110 (81–147)	200 (100-250)
Free erythrocyte protoporphyrin (μu/100 ml)	40 (14–79)	180 (30-600)

Modified from Cartwright and Lee[2]

the marrow's ability to respond to erythropoietin both remain intact. Although Ward[6,7] was unable to detect an inhibitor to erythropoiesis in such patients by an *in vivo* neutralization test, their method did not exclude the possibility of normal production of erythropoietin in response to anemia and a concurrent production of inhibitor. Lindemann[10] has recently demonstrated an erythropoietin-inhibiting factor in the urine of normal persons and of patients with aplastic anemia. His description of a simple method of independently quantitating both erythropoietin and erythropoietin-inhibiting factor in the same specimen should stimulate application of this technique to the anemia of chronic disorders.

3. **Abnormal Iron Metabolism.** Duodenal absorption of iron is decreased in this disorder. However, this does not contribute to the anemia since storage iron is adequate unless iron deficiency coexists.

Patients with the anemia of chronic diseases incorporate transferrin-bound iron normally into hemoglobin. This was first demonstrated by Freireich, et al.[11] in dogs with sterile inflammation. However, incorporation of hemoglobin iron administered as non-viable erythrocytes or as hemoglobin solutions was markedly impaired. This phenomenon has been termed "reticuloendothelial iron block," and has subsequently been confirmed in patients.[12,13] Typically, although utilization of iron as $^{59}Fe\ Cl_3$ is 70 to 90 percent (normal: > 75 percent), reutilization of ^{59}Fe as hemoglobin solutions was usually about 40 percent, with values as low as 4.6 percent. (normal: ~ 70 percent).[13] Whether or not the "reticuloendothelial iron block" is completely explained by deficiency of erythropoietin is an open question. Several lines of evidence bear on this:

(1) Gutnisky and Van Dyke[9] have shown that in rats with turpentine abscesses, an animal model of the anemia of chronic disorders, serum iron is lower than in control rats, and injection of erythropoietin makes it lower still, rather than raising it toward normal as would be expected if erythropoietin deficiency were the only abnormality.

(2) Lawrence, et al.[14] did not find a fall in serum iron when taking natives of high altitude down to sea level, as would be expected if low levels of erythropoietin were the cause of the hypoferremia seen in the anemia chronic disorders.

(3) Reynafarje, et al.[15] have shown that ascent to high altitude causes an increase in plasma iron turnover and red blood cell (RBC) iron turnover, and that descent from high altitude after erythrocytosis has developed, causes a decrease to values below normal. These changes are presumably due only to the change in erythropoietin levels. Several investigators[12,16,17] have found that these parameters are normal or elevated in patients with cancer and the anemia of chronic disorders, again suggesting that low erythropoietin is not a complete explanation of this anemia.

Thus the development of this anemia seems to be due to a mild shortening of RBC survival, perhaps due to metabolic products of the tumor or to an immunological phenomenon affecting either the cells or the reticuloendothelial system directly, to an impaired marrow response to anemia which appears to be due to low levels of erythropoietin, and to a defect in iron metabolism at the level of passage of catabolized hemoglobin iron through the reticuloendothelial system to transferrin. This last defect is not explained solely by low levels of erythropoietin.

The common pathogenetic pathway by which an essentially identical tripartite mechanism for anemia occurs in such different disorders as cancer, chronic infection, and rheumatoid arthritis remains unknown.

Therapy of this anemia has been largely unsatisfactory. Because of the morphological similarity to iron deficiency, iron therapy has been frequently attempted. This sometimes produces a slight improvement, presumably related to coexistent iron deficiency. Cobalt can partly correct the anemia[3] or at least increase the red cell mass, but since cobalt

appears to act by interfering with oxygen transport it is doubtful that any increase in tissue oxygenation results. Administration of purified erythropoietin, which is not yet available in suitable quantities, should correct at least part of the defect and alleviate the anemia. However, a glycoprotein with a molecular weight of 35,000 is likely to be antigenic in man and probably not suitable for therapy.

The only satisfactory method of treating the anemia of chronic disorders at this time is by correcting the underlying disease. An example of this method is given by the patient reported by Greenberg and Creger[18] whose RBC volume and ferrokinetic parameters returned to normal after resection of a renal cell carcinoma.

PURE RED CELL APLASIA (PRCA)

A very uncommon syndrome which has attracted attention in recent years is that of pure red cell aplasia, also known as erythroblastic hypoplasia or erythroblastopenic anemia. This syndrome is characterized by the absence of reticulocytes from the peripheral blood and of erythroblasts from the marrow and is distinguished from aplastic anemia by the absence of platelet and leukocyte abnormalities. The differential diagnosis of pure red cell aplasia as noted by DiGiacomo, et al.[19] includes a congenital form and a number of acquired post-infectious, toxic, nutritional, and idiopathic forms. The single most common association of this uncommon disorder seems to be with thymoma, this category including over 40 percent of the patients with PRCA reviewed by Jacobs and his associates.[20] A rarer paraneoplastic association of PRCA has been described with a variety of neoplasms other than thymoma. Mitchell, Pinn and Pegrum[21] found six such cases in the literature and reported one case of their own. In two of the patients they reviewed, a thymoma was also present. Of 449 patients with thymoma reviewed by Rubin and his coworkers,[22] 17 had "hypoplastic anemia."

In an extensive review of PRCA associated with thymoma, Hirst and Robertson[23] noted the following features:

1. Only one of 56 patients was less than 40 years of age. The syndrome tends to occur in females and it usually presents as anemia. The anemia may occur after thymectomy.

2. Occasionally tumors have been found when radiographic examination of the chest was negative. (Ellis and Gregg[24] state that almost all thymic tumors can be detected by postero-anterior lateral, and 20° oblique views, and lateral tomograms of the mediastinum.)

3. Most patients present with anemia alone, but a few also have thrombocytopenia or pancytopenia.

4. The anemia is usually normocytic but may be slightly macrocytic. Poikilocytosis was noted in one case. (Platzer[25] has reported a case with ovalocytosis.)

5. Usually the tumor was in the anterior or superior mediastinum or both, weighed less than 30 gms and was composed of mixed spindle cells and lymphocytes. Six tumors invaded local structures and two had distant metastases.

The syndrome most commonly associated with thymoma has been myasthenia gravis which Rubin[22] noted in 187 of 449 cases of thymoma he and his associates reviewed. Myasthenia gravis is discussed elsewhere in this symposium. Myasthenia and PRCA may occur in the same patient. The myasthenia may precede the anemia by many years and may have remitted at the time anemia develops. Acquired agammaglobulinemia has been seen in this syndrome,[26] and a case with both rheumatoid arthritis and agammaglobulinemia has been reported.[27]

An increased frequency of a positive Coombs' test and a positive test for lupus erythematosus (LE) are associated with this syndrome. Hirst and Robertson also noted a positive test for antinuclear factor in all seven of the cases they reviewed in which this test was reported.[23]

In the absence of specific deficiency, treatment with hematinics has been of no value, and transfusion has been the only effective form of palliative therapy.

Thymectomy appears to be the linchpin of curative therapy. Of the 56 cases reviewed by Hirst and Robertson, 25 had a thymectomy, in some cases before the appearance of anemia. No patient who did not have a thymectomy at some stage of the disease fulfilled their criteria for a good hematologic remission.

There is no evidence to suggest that removal of a thymus which does not contain a thymoma is of any value.[28,29] Only three of Hirst and Robertson's patients who had not had steroid therapy at some time in their course had a remission. The value of splenectomy was moot. Irradiation of the thymus had no effect on the anemia or the size of the tumor. These authors, in 1967, stated that "thymectomy should be the first method of treatment if possible. The signs of remission, if it is to occur, are to be expected within four weeks and should be sought in the marrow, as regeneration there may precede clinical remission by some time. This failing, prednisone or its equivalent should be given, in doses of 60 mg per day."[23]

Further therapeutic progress followed the elucidation of part of the pathogenesis of this disease. Large quantities of erythropoietin have been found in the plasma of patients with PRCA[32,35,36] suggesting that either an abnormality in the red cell precursors themselves, as in the congental PRCA of Diamond and Blackfan or in Fanconi's anemia, or a serum factor interfering with the effect of erythropoietin is pathogenetically involved. Early attempts to demonstrate an inhibitor of erythropoietin in serum or thymic extracts from these patients were unsuccessful. Such a factor was eventually shown by the *in vitro* inhibition of cell growth and proliferation of normal marrow,[30] by depression of normal erythropoiesis in the mouse,[31] and by suppression of stem cell colony formation in irradiated mice.[32] The association of PRCA with the several immune disorders and with the abnormal immunologic findings noted above have led investigators to speculate that PRCA may be an autoimmune disorder and that the serum factor may be an autoantibody.

In the period from 1967 to 1970, Krantz and Kao[33,34] and Safder, Krantz and Brown[35] reported three patients with PRCA, one of whom had a previous thymectomy. Apparently permanent hematologic remissions were obtained by limited courses of immunosuppressive therapy. In all three cases, incubating the patients' marrow in the absence of autologous serum increased the rate of erythropoiesis, and an IgG antierythroblast-nucleus antibody was found. The pre-remission IgG globulins of one of their patients inhibited heme synthesis by normal marrow while a similar fraction obtained post-remission failed to do so. Al-Mondhiry and his co-workers[36] demonstrated disappearance of an IgG inhibitor of erythropoiesis from serum and urine of a patient with PRCA after cure by thymectomy.

Most recently, Krantz[37] reported a case of PRCA which did not respond to cyclophosphamide. This patient was then treated with horse antihuman thymocyte gamma globulin (HAHTGG) as well as cyclophosphamide, and although therapy with HAHTGG was discontinued because of a reaction to the drug, a significant reticulocytosis, as had never been produced previously by splenectomy and therapy with prednisone or cyclophosphamide was obtained. Krantz noted that this patients' marrow responded less to erythropoietin *in vitro* than had the marrows of the three patients who had been treated successfully with immunosuppressive drugs and that several other unpublished cases of PRCA which had similar small increases in ^{59}Fe incorporation *in vitro* also failed to respond to immunosuppressive drugs alone.

It thus seems likely that PRCA, with or without thymoma, is an autoimmune disease and that an IgG antibody to autologous erythrocyte precursers is pathogenetically involved. Optimal therapy at the present time for patients with thymoma would seem to be thymectomy initially, and if remission does not occur, treatment with steroids, immunosuppressive agents, antithymocyte gamma globu-

lin or some combination of the three. Although as previously noted, thymectomy in the absence of apparent thymoma does not appear to be useful, perhaps this should be reevaluated in combination with immunosuppressive therapy.

POLYCYTHEMIA

The association of erythrocytosis with malignant disease is well documented. Although this condition has been associated with such non-neoplastic lesions as renal cystic disease[38–40] and hydronephrosis,[38,39] the remaining associations have been with neoplasia. These have included renal adenomas,[38] hypernephromas,[40–42] Wilms tumor,[43] cerebellar hemangioblastomas,[44–47] uterine leiomyofibromas,[48–50] pheochromocytomas,[51,52] adrenal adenomas,[53] virilizing ovarian tumors,[54] and hepatomas.[55–58] Erythrocytosis is an uncommon finding in these conditions, but is not rare. It has been reported to occur in 20 percent of cases of cerebellar hemangioblastoma,[44] in 10 percent of patients with hypernephroma,[40] and in 2.8 percent of patients with hepatoma.[57] Conversely, it has been reported that renal carcinoma occurs in about one percent of cases of polycythemia, when the occurrence of renal carcinoma in the general population is 0.003 percent.[59]

Paraneoplastic erythrocytosis may be defined as a significant increase in red cell mass, unassociated with abnormalities of oxygen delivery or increased circulating numbers of the other formed elements of the blood. Diagnosis requires exclusion of hemoconcentration, arterial oxygen desaturation, abnormal hemoglobins, and polycythemia vera.

The most recently proposed scheme for the regulation of erythropoiesis hypothesizes two circulating factors: a renal erythropoietic factor termed REF or erythrogenin, and a circulating serum substrate which is converted by REF to biologically active erythropoietin (ESF).[60] REF is itself erythropoietically inactive and is antigenically distinct from ESF. Elevated levels of ESF have been reported in plasma from patients with hepatocellular carcinoma,[56] with hypernephroma, and with renal cysts,[40,61] and in cases of Wilm's tumor, hydronephrosis, neuroblastoma and cerebellar hemangioblastoma.[61] The elevation of ESF in these cases could have been secondary to abnormal production of either REF or substrate, to some abnormality of their interaction, or to decreased inactivation or removal of REF, substrate or active ESF. Extracts of renal cell tumors,[61] uterine leiomyomas[50] pheochromocytomas,[51] and Wilm's tumors,[43] and of cyst fluid from cerebellar hemangioblastomas[47] and renal cysts[40] have been shown to have erythropoietic activity in a standard mouse bioassay. Unfortunately, the bioassay as usually done will not differentiate increased levels of REF or substrate from increased ESF itself. Gordon and his associates[58] have published a study of a patient with hepatocellular carcinoma and polycythemia in whose plasma they found elevated levels of bioactive ESF. They also found that the hepatoma contained substrate for REF but did not have any ESF activity itself. Furthermore, normal liver from their patient destroyed ESF activity, while hepatoma tissue did not. If substrate is normally produced in appropriate quantity by the liver, and erythrocytosis in patients with hepatoma is caused by excessive production of substrate, erythrocytosis associated with renal lesions may be due to increased production of REF, but data verifying this is not yet available.

The frequency of increased levels of ESF is considerably underestimated by hemoglobin levels alone. Murphy, et al.[61] found elevated levels of plasma ESF in approximately 30 percent of patients with a variety of renal lesions; polycythemia was present in about one-third of these patients. Some of the elevated levels of ESF were probably secondary to anemia, but in addition, bleeding and the anemia of chronic disorders would have reduced the expression of polycythemia even when true ectopic or autonomous erythropoietin production was present.

The mechanism of erythrocytosis in this disorder is clearly different from that of polycythemia vera in which erythropoietin levels are not increased.[62]

DISORDERS OF OTHER BLOOD CELLS

Platelets:

Platelets were recognized as cellular elements of the blood late in the 19th century, and reliable methods for their counting have been available only for the last few decades. The association of thrombocytosis with malignancy was not well documented until the late 1960's. Non-hematological malignancies have been found in 35 to 65 percent of unselected patients with thrombocytosis.[63,64] Silvis and his associates[65] found that 60 percent of patients with lung cancer had thrombocytosis and that the platelet count did not correlate with the hemoglobin, duration of disease, acute bleeding episodes, or the presence of metastasis; nor was thrombocytosis associated with a significant increase in thromboembolic disease.

The mechanism of thrombocytosis in these patients is not known. Thrombopoiesis appears to be regulated by a circulating hormone, thrombopoietin, which causes an increase in the number and size of megakaryocytes in the bone marrow.[66] Increased numbers of magakaryocytes have been found in the marrow of patients with cancer by Harker and Finch.[67] These authors interpret the decrease of megakaryocyte volume in the face of increased numbers as indicating that differentiation of megakaryocytes from the precurser pool in these patients is caused by factors apparently unrelated to hemostatis. It has been suggested that thrombocytosis is related to tumor necrosis, although Silvis, et al.[64] did not observe a consistent rise in platelet count with tumor necrosis from x-ray or chemotherapy.

Thrombocytopenia is a well-known complication of hematological malignancy, particularly the acute leukemias; however, thrombocytopenia, like thrombocytosis, is a recently recognized complication of non-hematological malignancy.[68] In a hospital survey of 7,750 patients, 393 patients with platelet counts less than 150,000 were found.[69] Among these, the most frequent single cause of thrombocytopenia was therapy for malignant disease, but 14 patients with non-hematological malignancy had thrombocytopenia prior to therapy. The mean platelet count in this group was 69,000. All cases had disseminated disease, some with bone marrow involvement, and one had intravascular coagulation with an improvement of the platelet count when the patient was treated with heparin.

Myelophthisis and intravascular coagulation may not account for all such cases, however. Brodie et al.[70] reported two patients with carcinoma of the lung and thrombocytopenia in which neither of these mechanisms could be documented. One had increased megakaryocytes in the marrow, a markedly shortened platelet survival time, and no evidence of fibrin split products or other coagulation abnormality. The second had increased megakaryocytes in the marrow and no evidence at autopsy of bone marrow involvement or platelet or fibrin deposition in vessels after nine months of thrombocytopenia. Neither patient had been exposed to drugs or chemicals known to cause thrombocytopenia. The authors postulated an autoimmune mechanism for this phenomenon.

Leukocytes:

The occurrence of leukemoid reactions in patients with non-hematological malignancy is well known.[4,71] It usually occurs in patients with widespread bone metastases, but occasionally occurs with limited disease. The picture may suggest myelocytic leukemia, and Wintrobe[7] suggests that the leukocyte alkaline phosphatase may be helpful in distinguishing this from a leukemoid reaction, as the score is low in myelocytic leukemia.

Mild-to-moderate eosinophilia, without other apparent cause, also occurs frequently in patients with cancer.[4]

Persistent leukopenia with leukocyte

counts between 2,500 and 4,000/mm^3 has been noted in patients with cancer. This was invariably accompanied by moderate-to-severe anemia.[4]

When not related to marrow involvement by tumor, the mechanism is not known for either leukemoid reactions or leukopenia in malignancy.

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METABOLIC SYNDROMES ASSOCIATED WITH NEOPLASIA

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INTRODUCTION

Clinicians have recognized metabolic presentations of neoplastic disorders in only the past few decades. This recognition has opened new avenues of investigation in clinical endocrinology. Many of these syndromes have been shown to be related to an uninhibited secretion of a specific hormone by neoplastic tissues usually considered to be non-endocrine: an ectopic hormonal syndrome. The pathogeneses of other syndromes to be discussed remain in doubt and the questions they raise should provide further fruitful areas of investigation in the ensuing years.

Hypercortisolism (Cushing's Syndrome)

In 1928, W. Hurst Brown reported a case of what has now become known as the ectopic adrenocorticotropic hormone (ACTH) syndrome, three years before Harvey Cushing described the syndrome which now bears his name.[1] Brown's patient was a woman with a one-centimeter oat cell carcinoma of the lung and "the diabetes of bearded women." An endocrine pathogenesis for this syndrome was first postulated when Leyton and his associates reported patients with small cell thymic tumors and adrenocortical hypertrophy associated with features of Cushing's syndrome.[2] Since that time, there have been well over one hundred cases of this syndrome described in the literature, and several reviews have appeared on the subject.[3,4]

The clinical manifestations of the ectopic ACTH syndrome are similar to those of classical Cushing's disease due to enhanced pituitary ACTH secretion. However, some clinical differences can provide important differential diagnostic clues. Significant edema of the lower extremities is more common in the ectopic ACTH syndrome. Profound electrolyte abnormalities and glucose intolerance, rather than alterations of physical appearance, frequently dominate the clinical picture.

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It is also difficult to differentiate a patient with the ectopic ACTH syndrome from a patient with a functioning adrenocortical carcinoma. Both of these entities may follow a rather fulminant course and have associated profound metabolic abnormalities. The dexamethasone suppression test is often but not always negative in each instance.[5] ACTH assays are of considerable value in making this differentiation, but they may be difficult to obtain routinely. The patient who develops rapidly progressive Cushing's syndrome along with hyperpigmentation is likely to have the ectopic ACTH syndrome, although in this clinical setting a pituitary tumor must be excluded. Grant Liddle's group has demonstrated melanocyte-stimulating activity in tumor extracts in excess of what could be expected from the ACTH content alone.[6,7]

On the basis of chemical, immunological, and biological analyses, both the serum and the tumors of patients with the ectopic ACTH syndrome have been found to contain a substance which is indistinguishable from normal pituitary ACTH.[4,7,8] Melanocyte-stimulating-hormone-like (MSH-like) activity has been demonstrated in tumor extracts and in serum obtained from patients with the ectopic ACTH syndrome associated with intense hyperpigmentation.[6,7,9]

Upton and Amatruda have recently presented evidence that a tumor responsible for the ectopic ACTH syndrome produced, in addition to ACTH, a peptide with corticotropin-releasing-factor (CRF) activity similar to that produced by the hypothalamus. These authors elegantly demonstrated the CRF-like activity by isolating a small peptide from the oat cell carcinoma and assaying the adrenal stimulating activity of the peptide in hypophysectomized rats. No direct adrenal stimulating activity by this small peptide was observed.[8]

The ectopic ACTH syndrome has been described in many types of tumors, most of which are malignant. The most common primary tumor is oat cell or small cell carcinoma of the lung which accounts for approximately 40 percent of the cases. According to Azzopardi and Williams, endocrine tumors of foregut origin, such as thymomas, medullary carcinomas of the thyroid, parathyroid carcinomas, bronchial carcinoids, and pancreatic carcinomas (many of which are of islet-cell origin) comprise the second most common group of tumors implicated in the ectopic ACTH syndrome. Pheochromocytomas and related tumors of neural crest origin and certain uncommon ovarian tumors have also been implicated.[10]

Surgical extirpation of the responsible tumor is indicated when the tumor is benign or localized. If the neoplasm is not resectable or if faced with recurrent disease, surgical adrenalectomy has been frequently performed. With the recent introduction of inhibitors of adrenocortical biosynthesis such as metapyrone, o,p'—DDD and aminoglutethimide, pharmacologic manipulation of this syndrome has become a more feasible means of management.[11–13] The ACTH activity of these tumors is on rare occasions suppressible with dexamethasone.[5–11]

Hypercalcemia

Hypercalcemia is an extremely common accompaniment of neoplastic disease. One must divide the hypercalcemic patients into two distinct groups. The first of these groups includes patients who have invasion of bone by their tumors. It is presumed that the hypercalcemia in this clinical setting is the result of direct osseous erosion by tumor tissue. The second group of patients consists of those who have hypercalcemia with no demonstrable bony metastases. These tumors frequently have been shown to secrete a parathormone-like (PTH-like) substance. It should be noted that no large prospective studies have been done with patients suspected of having a PTH-producing tumor, employing bone scanning procedures to add to the degree of certitude that metastatic bone lesions are absent.

The first case of hypercalcemia of malignancy associated with hypophos-

phatemia was reported by Gutman and his associates in 1936.[14] Speculation that the parathyroid hormone might be produced ectopically was first made by Fuller Albright in 1941.[15] Several groups subsequently described the correction of hypercalcemia with hypophosphatemia in certain patients after removal of their malignant tumors.[16,17] Tashjian and his associates demonstrated a material immunologically similar to PTH in extracts of tumors from several patients.[18] More than one immunologically identifiable PTH has been extracted from some tumors.[19] There is evidence that the biologic activity of these different PTH's may vary. Bovine parathyroid tissue has been shown to synthesize an intracellular "proparathormone" which is immunologically distinct from circulating PTH.[20] One can speculate that the immunologically variable PTH extracted from tumor tissue represents a variety of macromolecular PTH precursor peptides.

The symptoms of hypercalcemia include nausea, vomiting, anorexia, a peculiar taste in the mouth, constipation, polyuria, weight loss, weakness, and mental confusion progressing to stupor. Severe progressive hypercalcemia may lead to oliguria, azotemia, and coma. Patients may have depressed muscle function with hypotonicity, depressed tendon reflexes, and transient palsies. Ectopic calcifications may be found in the conjunctiva, cornea, or other soft tissues. Characteristic electrocardiographic changes include a prolonged PR interval and a shortened QT duration. Tachycardia and life-threatening arrhythmias may occur.

The differentiation between hypercalcemia caused by primary hyperparathyroidism and that caused by ectopic PTH production is quite difficult, and the laboratory and clinical features are very similar (See Table). The hypercalcemic patient is perhaps more likely to have a nonparathyroid tumor if he has evidence of weight loss, if the serum calcium concentration exceeds 14 mg/100 ml while the serum chloride is less than 102 mEq/l and if he is anemic. On the other hand, a patient is more likely to have a parathyroid tumor or hyperplasia if there is a history of renal stones, if there is radiographic evidence of subperiosteal bone resorption, if the patient is female, and has a serum chloride concentration greater than 102 mEq/l.[21] Many of these differences are related to the relatively rapid course of the carcinoma in contrast to the more chronic course of the nonmalignant disease.

LABORATORY AND CLINICAL FEATURES OF HYPERCALCEMIA CAUSED BY PRIMARY HYPERPARATHYROIDISM AND THAT CAUSED BY ECTOPIC PTH PRODUCTION*

	PRIMARY HYPERPARATHYROIDISM	ECTOPIC HYPERPARATHYROIDISM (PSEUDOHYPERPARATHYROIDISM)
Sex Dominance	Females	Males
Weight Loss	−	+
Anemia	−	+
History of renal stones, ulcer disease, and/or bone pain	+	−
Radiologic evidence of subperiosteal bone resorption	+	−
Serum Ca^{++}	< 14 mg %	> 14 mg %
Serum Cl^{-}	> 102 mEq/l	< 102 mEq/l

*The differential diagnosis of primary hyperparathyroidism and the hyperparathyroidism due to the ectopic production of parathyroid hormone-like material by neoplastic tissue. Based on data provided by Lafferty (21), this Table is intended to provide the clinician with guidelines useful in making this critical distinction.

PTH-producing neoplasms originate most frequently in the kidney. Epidermoid carcinomas of the lung and other organs constitute the other major group. There have been scattered reports of hepatic, pancreatic, urinary bladder, and ovarian carcinomas also causing hypercalcemia.[21,22] Resection of the primary tumor often causes reversion of the calcium level to normal, and recurrence of tumor or the appearance of metastases is associated with the return to elevated serum calcium levels.

Until very recently the treatment of hypercalcemia consisted of increased fluid intake to promote diuresis, salt to promote calciuresis, and the administration of high doses of corticosteroids. Chelating agents such as EDTA and complexing agents such as high doses of phosphates and sulfates have also been used. Because these measures are only transiently effective and the associated complications of soft tissue calcification are often severe, their use is recommended only in life-threatening emergencies (*e.g.*, arrhythmias). The recent introduction of mithramycin into clinical medicine has facilitated control of serum calcium levels and allowed greater patient comfort despite progression of the neoplastic process.[23,24] The use of calcium-free peritoneal dialysis, furosemide, actinomycin-D, and calcitonin are currently being investigated.

Hyponatremia (Schwartz-Bartter Syndrome)

Although asymptomatic hyponatremia has been a well established entity for many years, it was not until 1957 that William B. Schwartz and his colleagues suggested that this was due to the inappropriate secretion of antidiuretic hormone (ADH).[27] They reported on two patients with carcinoma of the lung. The syndrome of inappropriate ADH secretion is now known to occur most frequently in patients with nonmalignant intracranial or intrathoracic diseases.[28,29] In 1963, Amatruda and his associates found ADH-like activity in a tumor extract from a carcinoma of the lung.[30] Subsequently, other investigators have extracted similar material from other tumors.[29,31]

The following features comprise the syndrome of inappropriate ADH secretion: hypoosmolality of the serum in association with hyperosmolality of the urine, hyponatremia with hypernaturesis, the absence of edema, normal renal and adrenal function, and reversion toward normal with fluid restriction. Bartter and Schwartz admonished that "a urine which is less than maximally dilute in the presence of plasma hypotonicity provides clear evidence that there is a defect in water excretion." They also suggest searching for this syndrome in adult patients with hyponatremia and blood urea nitrogen levels less than 10 mg/100 ml.[32]

Hypernaturesis is not an invariable feature of this disorder. Severe depletion of total body sodium may have occurred in the very disabled patient by the time he comes to the attention of a physician.[32]

The paradox of hypernaturesis in the face of hyponatremia has generated several explanations. Neither the concept of aldosterone suppression nor that of enhanced glomerular filtration resulting from expanded extracellular fluid volume has been supported. The most attractive suggested mechanism to explain this paradox is the suppressed proximal tubular reabsorption of sodium ion in response to an expanded extracellular fluid volume. This is the "third factor" effect, a well established principle of renal physiology, probably mediated through local (renal) hormonal events.[32]

Patients may have no symptoms until the serum sodium is profoundly low (*e.g.*, 110 mEq/l). When this occurs, symptoms referable to water intoxication may appear. Loss of appetite, nausea, vomiting, irritability, and personality changes can be early signs. Neurologic abnormalities such as weakness or loss of reflexes progressing to stupor and convulsive episodes are late effects.

The greatest number of cancer patients with ectopic ADH production have been those with oat cell or anaplastic carcinomas of the lung. A large portion

of the remaining patients have primary or metastatic intracranial neoplasms of various sorts. The secretion of normal (pituitary) ADH induced by increased intracranial pressure may be an operative mechanism in these cases. Occasional reports of the syndrome in association with carcinoma of the duodenum, pancreas, or thymus, and with Hodgkin's disease, or reticulum cell sarcoma have appeared.[31,33] Hyponatremia has been related to vincristine therapy in an infant with a rhabdomyosarcoma.[34]

Treatment of this syndrome is restriction of water intake. In the critically ill patient with severe hyponatremia and neurologic disability, temporary benefit may be seen with the administration of hypertonic saline or potent mineralocorticoids.

Hypoglycemia

Malignant tumors of the beta cell of the pancreatic islet (insulinomas) frequently present with hypoglycemia related to an enhanced uncontrolled production of insulin. Efforts toward the diagnosis of insulinoma have recently been reviewed.[35,36] Effective therapy for this tumor is available.[37]

In 1929, Nadler and Wolfer reported a patient with hepatic carcinoma and hypoglycemic attacks.[38] Since that time, over two hundred nonpancreatic tumors associated with hypoglycemia have been reported. The largest group of these tumors are retroperitoneal sarcomas or mesotheliomas, with fibrosarcomas being the most common. Neurofibromas, rhabdomyosarcomas, and lymphosarcomas have also been reported. In each of these cases, the tumors were massive, usually weighing over 2000 grams before clinically significant hypoglycemia occurred. Other tumors which have been associated with hypoglycemia are hepatic and adrenocortical carcinomas.[7,39–43]

The symptoms of hypoglycemia consist of headache, diminished visual acuity, confusion, and varying neurological and behavioral abnormalities. Sweating, tachycardia, and extreme hunger are relatively rare in this syndrome because these symptoms tend to occur with a rapidly falling blood sugar rather than the sustained hypoglycemia that one frequently sees in this syndrome.

The pathogenesis of this syndrome is obscure. A material with insulin-like activity rarely has been demonstrated in the circulation of these patients or in tumor extracts. The various theories of the pathogenesis of this syndrome have been reviewed by Lipsett.[44]

Since these tumors tend to be massive and slow growing, the symptoms of hypoglycemia may be alleviated for considerable lengths of time by even partial resection of the responsible tumor. Radiation therapy or chemotherapy also may have beneficial effects. Diazoxide taken by mouth or injected glucagon are of benefit in supporting the blood sugar level.[43]

Ulcerogenic Tumors

In 1955, Zollinger and Ellison described a syndrome of severe gastric hypersecretion and intractable peptic ulceration associated with noninsulin secreting adenomas of the Islets of Langerhans.[45] Numerous reports of other patients have been described since then, some of whom manifest severe diarrhea and hypokalemia. A material with gastric secretory activity has been extracted from these pancreatic tumors and from their metastases.[46,47] This material has been found to have the same amino acid composition as normal (antral) gastrin.[47,48] Patients with the Zollinger-Ellison syndrome have been shown to have marked hypergastrinemia.[49] Using a fluorescein-labeled antibody to human gastrin, various investigators have recently demonstrated the presence of gastrin in the normal human delta cell of the pancreatic islet.[50,51] This suggests that these tumors are neoplasms of the delta cell of the pancreatic islet.

Thyrotoxicosis

Hyperthyroidism has been associated with hydatidiform mole or choriocarcinoma since 1955.[52] The normal human placenta produces a material with thyrotropic activity called chorionic thyrotropin.[53] A thyrotropic hormone differ-

ent from chorionic thyrotropin has been demonstrated in extracts from each of two hydatidiform moles removed from patients with this disease and life threatening thyrotoxicosis.[54] The name *molar thyrotropin* has been given to this peptide. Thus, there are four known polypeptides with thyrotropic activity: pituitary thyrotropic hormone (TSH), the long acting thyroid stimulator (LATS), chorionic thyrotropin, and molar thyrotropin.

Precocious Puberty

Precocious puberty has been noted in a number of children with hepatoblastoma or trophoblastic tumors.[55] The gonadotropin produced in these children is similar to luteinizing hormone (LH), (ICSH), or chorionic gonadotropin and is dissimilar to follicle stimulating hormone (FSH). Pathologic findings include testicular interstitial cell hyperplasia and absence of testicular duct proliferation.[41,44] In addition to the enlarged penis, an advanced bone age is seen clinically. This syndrome is not detected in female children because the target organ for LH, the ripe ovarian follicle, is not present. The measurement of gonadotropins in girls with hepatoblastoma has not been done.

Gynecomastia

Gynecomastia is noted in some patients with bronchogenic carcinomas of varying histology. The abnormal gonadotropin presumed to be produced in this syndrome has not been adequately characterized.[44,56]

Galactorrhea

Turkington has recently demonstrated the ectopic production of prolactin in a woman with a hypernephroma and galactorrhea and in a man with an undifferentiated bronchogenic carcinoma. Cells from the hypernephroma were shown to elaborate prolactin into tissue culture medium.[57] With the recent development of immunoassays for prolactin, our understanding of normal and abnormal lactation should advance considerably in the next several years.

Virilization

Virilization of the female has been reported in a number of adrenal and ovarian neoplasms and can be associated with a variety of metabolic abnormalities. Ovarian tumors associated with virilization include arrhenoblastomas, adrenal rest tumors, Leydig cell tumors, granulosa cell tumors and Brenner tumors.[58]

Novak and his coworkers have recently described a patient with a papillary mucinous cystadenoma of the ovary with stromal Leydig cells who developed virilization during her second pregnancy. A review of the literature at that time revealed 24 other cases of virilization during pregnancy. Tissue had been obtained at surgery or autopsy from all but one of these patients, and each had an ovarian tumor of varying histopathology. In several patients studied, there were elevated plasma testosterone levels or increased 17-ketosteroid excretion.[59]

Multiple Endocrine Neoplasia (Men)

There are two syndromes of familial adenomatosis which have been referred to as multiple endocrine neoplasia, types I and II.[60] Type I MEN is most often characterized by adenomas of the anterior pituitary, the parathyroids, and the pancreatic islet cells. These tumors are generally benign. The parathyroid adenomas are the most frequently functioning tumors in this group, though hypoglycemia or evidence of pituitary malfunction may dominate the clinical picture. Subcutaneous lipomas occur in approximately 50 percent of the cases. Bronchial carcinoid tumors occur in this syndrome with greater-than-chance frequency. Nodular hyperplasia of the thyroid, ovaries, and adrenal glands is seen, but this may be related to the pituitary adenoma. Ulcer disease is commonly noted in these patients and probably is associated with hypercalcemia, though cases of associated Zollinger-Ellison syndrome have been reported. The mode of inheritance of this syndrome is probably autosomal dominant with a high degree of penetrance.[61] Approximately 36

afflicted families have been reported since Wermer's paper in 1954. In screening families with suspected patients, the most useful information comes from a careful history and serum calcium determinations.[62]

Type II MEN is characterized by the familial occurrence of pheochromocytoma, medullary carcinoma of the thyroid, and hyperplasia or adenoma of the parathyroid glands. Parathyroid hyperplasia probably represents a compensatory response to calcitonin secretion by the medullary carcinoma of the thyroid. Multiple ganglioneuromas are frequently found on the lips, tongue, conjuctiva, and throughout the entire gastrointestinal tract.[63,64] (Figs. 1, 2a, 2b) The patients may have characteristic facies with protruding ears, prognathia, and thick everted eyelids. (Figs. 3a, 3b). The body habitus is suggestive of Marfan's syndrome. Slit-lamp examination may reveal myelinated nerve fibers in the cornea.[63,65]

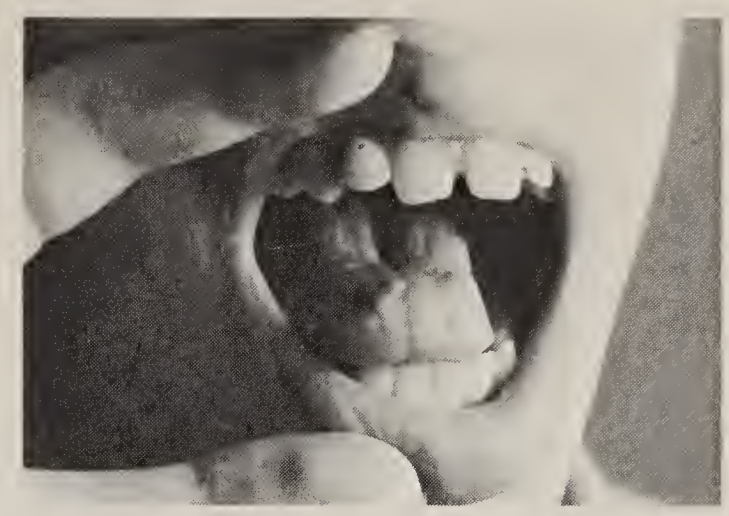
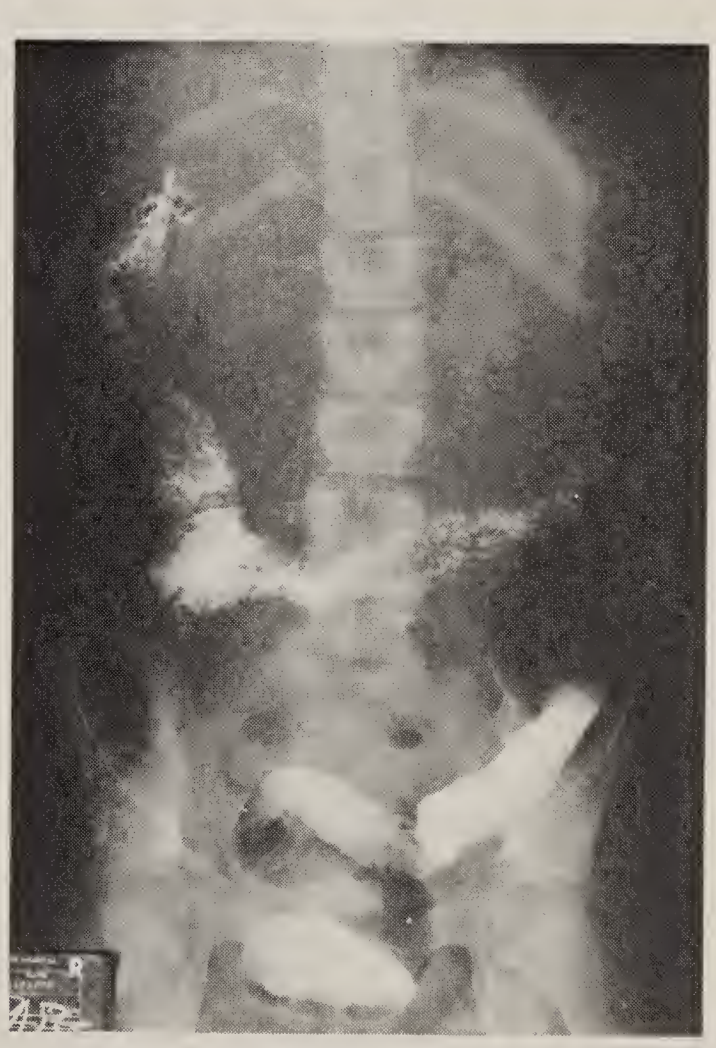


Fig. 1—Multiple lingual ganglioneuromas (mucosal neuromas) in a patient with MEN II. *(Photograph courtesy of Dr Charles P. Perlia.)*

Intractible diarrhea is usually the most prominent clinical feature of this disease. In addition to calcitonin, these medullary thyroid carcinomas, frequently with amyloid stroma, secrete prostaglandins and perhaps other hormones which increase bowel activity.[66] This clinical picture is in sharp contrast to sporadic cases



Figs. 2a and 2b—Barium enema examination of a child with MEN II. Note (a) the abnormal haustral pattern in the dilated colon, and (b) the thickened mucosal folds on the postevacuation film. No colonic diverticula are noted.

Figs. 3a and 3b—MEN, Type II. Two unrelated adolescents with strikingly similar facies. Note the prognathic jaws, thickened fleshy lips, and early eversion of the tarsal plates. *(Photographs courtesy of Dr. Charles P. Perlia.)*

of medullary thyroid carcinoma in which amyloid is not seen and in whom associated tumors and diarrhea are infrequently noted.[67,68]

It is important to note that the tumors of MEN Type II tend to be multicentric in origin. Unilateral adrenalectomy is often not adequate therapy for patients with pehochromocytoma, and total thyroidectomy must be performed for medullary thyroid carcinoma. The practicing physician should be able to recognize afflicted families and observe members closely for development of hypertension or neck masses. Otherwise asymptomatic members in afflicted families have been discovered by screening the blood and urine for calcitonin content.[69] Serum histaminase levels have been correlated with metastases and residual tumor after operation.[70]

Though frequently called "Sipple's syndrome," none of the six cases discussed by Sipple had medullary carcinomas of the thyroid.[71]

CONCLUSION

A neoplasm may be thought of as a group of metabolically active cells producing both normal and abnormal products. The syndromes discussed in this presentation are manifestations of tumor products with significant biologic activities. It is hoped that the early detection of these metabolic products of neoplasms will result in the earlier identification of affiicted patients and that this, hopefully, will result in improved therapeutic modalities and increased meaningful survival.

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RENAL, GASTROINTESTINAL, AND MUSCULOSKELETAL MANIFESTATIONS OF NEOPLASIA

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INTRODUCTION

Other articles in this symposium have analyzed the metabolic, hematologic, and neurologic aspects of the remote manifestations of neoplasia. In this paper, we shall discuss the renal, gastrointestinal, and musculoskeletal manifestations of neoplastic diseases.

RENAL MANIFESTATIONS OF NEOPLASIA

Nephrotic Syndrome

Lee and his coworkers described the association of cancer and the nephrotic syndrome.[1] In their retrospective review of patients seen by them over a ten-year period, 10.9 percent of the cases of nephrotic syndrome developed cancer in close temporal relationship to the onset of nephrotic syndrome. Cases of amyloidosis and renal vein thrombosis were excluded from their series. All of their patients had carcinomas of varying histology and sites of origin. Kidney biopsies were obtained in ten of their cases, either during life or at necropsy. In eight of these ten biopsies, membranous glomerulonephritis was seen on light and electron microscopy. One case each of "lobular glomerulonephritis" and lipoid nephrosis (with fusion of epithelial foot processes on electron microscopy) complete their series.

Immunofluorescent studies were not performed on their material. These authors speculated, however, than an antigen-antibody complex might be deposited along the glomerular basement membrane inducing the glomerular disorder immunologically. This hypothesis takes on additional significance with the recent evolution of our concepts of tumor specific antigens.

Subsequent series of cases of nephrotic syndrome have failed to verify this incidence of cancer in this nephropathy. A cause-and-effect relationship between malignancy and the nephrotic syndrome is supported in the case of a sixty-year-old man in whom a nephrotic syndrome of three months' duration was reversed with removal of his gastric carcinoma.[2] This patient has remained free of both diseases for ten years. Further, three cases of relapsing nephrotic syndrome have recently been presented in whom exacerbation of the nephrotic syndrome was associated with the exacerbation of Hodgkin's disease in each case.[3] These authors were able to review fourteen cases of nephrotic syndrome in association with active Hodgkin's disease.

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Loughridge and Lewis have presented three cases of nephrotic syndrome, two in patients with lung cancer and one in a woman, apparently free of cancer, five years after a radical mastectomy.[4] Though the renal histology varied between cases, membranous changes were detected in each. Renal tissue from one case of bronchogenic carcinoma was subjected to immunofluorescent analysis. A "lumpy" distribution of immunoglobulin-G (IgG) was demonstrated along the glomerular basement membrane. This is characteristic of immune deposit diseases; i.e., antigen-antibody complexes formed in the circulation are deposited along the filtering network of glomerular basement membrane. Poststreptococcal glomerulonephritis, quartan malaria, and secondary syphilis are associated with similar glomerular lesions.[5,6] After this patient's death, the antibody was eluted from the renal tissue. This antibody was shown to be identical with an antibody present in the patient's serum obtained during life. Further, this antibody reacted with membrane antigens on cells of the patient's lung cancer and was not absorbed by prior reaction with the patient's normal lung or kidney tissue or other tumor cells.[7] This suggests a tumor antigen specific for this cancer. Thus, five years later, the hypothesis of Lee and his associates seems to have been verified.

Renal Tubular Acidosis (RTA)

Several mechanisms of defective urinary acidification have been defined.[8,9] The distal type of RTA is associated with impaired excretion of hydrogen ions. This form of RTA can occur in hypergammaglobulinemic states such as those which might occur in macroglobulinemia, multiple myeloma, or other disorders associated with enhanced gammaglobulin production.[10] Distal RTA may also be associated with severe renal potassium wasting.

Hypokalemic Nephropathy

A nephropathy characterized by polyuria, polydipsia, mild azotemia and impaired renal concentrating capacity has been associated with prolonged hypokalemia. Neoplastic entities which may contribute to hypokalemia include some forms of Cushing's syndrome, adrenocortical diseases such as Conn's adenoma, villous adenoma of the colon and various disorders associated with diarrhea (*vide infra*). Vacuolization of the proximal tubular epithelium is characteristic.

Hypercalcemic Nephropathy

Hypercalcemia is commonly seen in neoplastic disorders, the mechanisms of which are discussed elsewhere in this symposium. Injury to the distal convoluted tubule and collecting ducts is associated with polyuria in the early stages of hypercalcemia. Ultimately, calcified casts form in these distal structures with resultant obstruction, stone formation, interstitial injury and severe renal failure. The rapidity with which these complications occur depends upon the duration and rate of development of the hypercalcemia. The patient with normal underlying renal function who develops hypercalcemic nephropathy acutely is likely to do quite well with the usual management for acute renal failure and measures directed toward reducing the serum calcium level. The patient with chronic asymptomatic hypercalcemia, however, is commonly insidiously robbed of his renal function and frequently presents clinically with a picture of chronic renal failure save for a surprisingly high serum calcium level.

Hyperuricemic Nephropathy

Probably as a result of rapid nucleic acid turnover, hyperuricemia is a common accompaniment of the myeloproliferative disorders, lymphomas, and myelomatoses. As the glomerular filtrate passes through the tubules, the solutes are concentrated and the filtrate acidified. When the pH drops below the pK for uric acid (5.5), soluble urate ion is transformed to insoluble uric acid, and precipitation in the distal intrarenal structures, renal pelvis, or ureters can ensue. As in hypercalcemic nephropathy, hyper-

uricemic nephropathy can occur in acute and chronic forms.

The xanthine oxidase inhibitor, allopurinol, has come into popular usage in the last decade. By blocking this enzyme, synthesis of uric acid is inhibited and the more soluble products, xanthine and hypoxanthine accumulate and are excreted. Allopurinol is a relatively safe agent useful in controlling chronic hyperuricemia and in the prophylactic management of potential hyperuricemia when initiating therapy in the disorders mentioned above.[11,12] It must be noted, however, that the metabolic fate of 6-mercaptopurine (6-MP) useful in the acute leukemias and azathioprine (which is converted to 6-MP) is dependent upon xanthine oxidase mediated conversion to 6-thiouric acid. Thus, when using either of these agents in combination with allopurinol, one must modify the dosage of 6-MP or azothioprine in order to avoid enhanced toxicity.[13]

GASTROINTESTINAL MANIFESTATIONS OF NEOPLASIA

Diarrhea and Malabsorption

Profound diarrhea frequently resulting in malabsorption is commonly noted in patients with medullary carcinoma of the thyroid gland. Zollinger-Ellison tumors and villous adenomas of the colon are also associated with profuse watery diarrhea. Carcinoid tumors and the relationship of lymphomas to the malabsorption syndrome will be discussed below.

Carcinoid Syndromes

Though carcinoid tumors have been recognized since the nineteenth century, the association of these tumors with a fascinating pattern of multisystem dysfunction has emerged in only the last two decades. Thornson and his associates called attention to malignant carcinoid tumors of the small intestine associated with hepatic metastases, fibrotic right-sided endocarditis, diarrhea, flushing, and bronchoconstriction.[14] This has become known as the classical carcinoid syndrome. A number of variant syndromes have been recognized in recent years and together with the classical syndrome merge into the carcinoid spectrum.[15] The unique features of these variants are summarized in the Table.

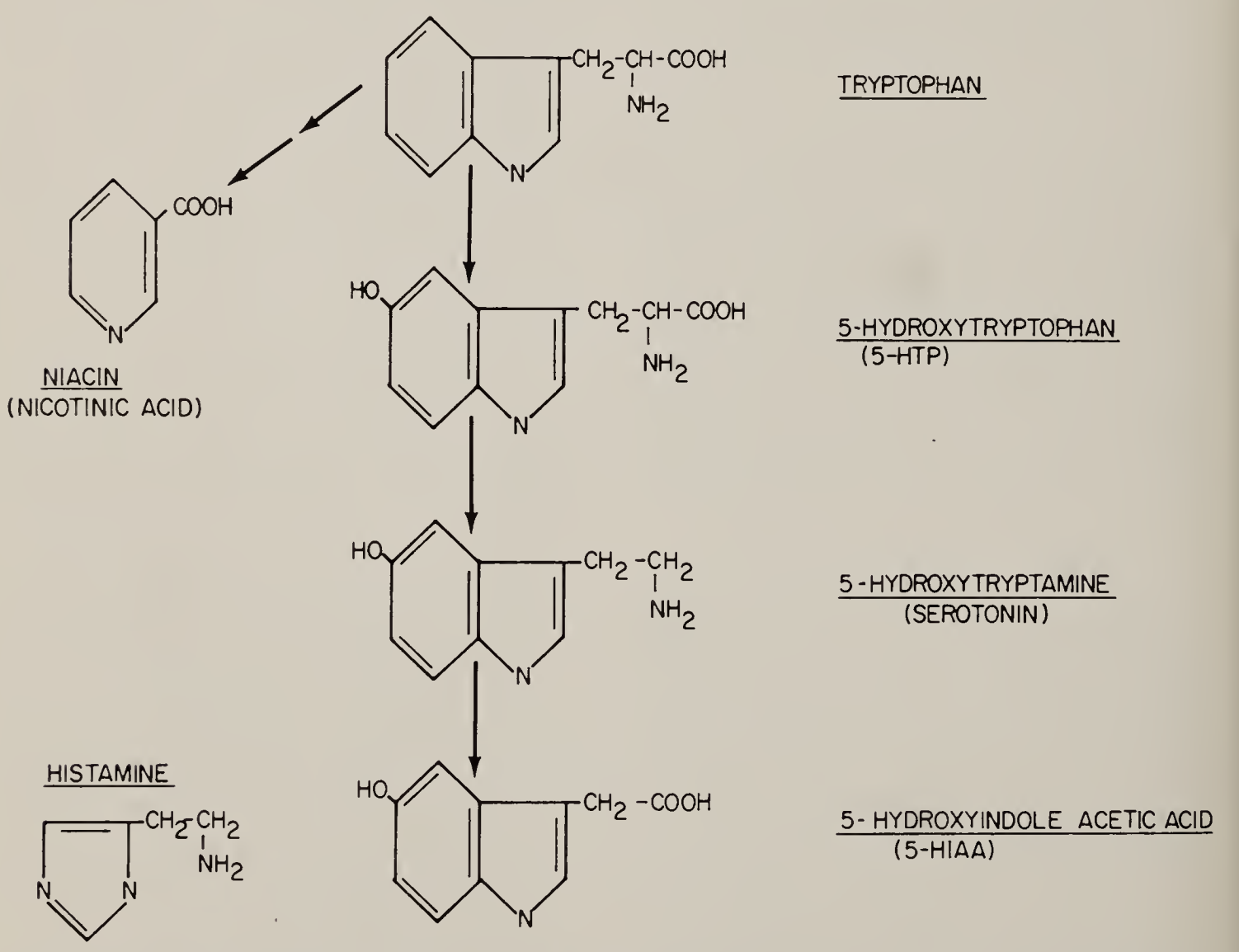
Evidence that these tumors are pharmacologically active was supported by Lembeck's discovery of a high serotonin content in one of these tumors.[16] Sjoerdsma and his associates demonstrated the very high urinary excretion of the end product of serotonin metabolism, 5-hydroxyindoleacetic acid (5-HIAA) in six patients with the malignant carcinoid syndrome.[17] These investigators also determined that so much dietary tryptophan was directed into this metabolic pathway that only small amounts were available for protein anabolism and for conversion to niacin. These authors concluded that the pellegra-like eruptions seen in this carcinoid syndrome could be accounted for in this manner (see Figure).

Defective metabolism of the indoles does not account for all manifestations of the carcinoid syndromes. Current concepts suggest that the flush is mediated through the kinin system. The inert alpha-2 globulin kininogen is converted to lysyl-bradykinin and finally bradykinin through the action of kalikrein and an aminopeptidase. The evidence for this association has recently been reviewed.[18,19] Melmon has encouraged the continuing search for other pharmacologically active substances in these tumors and suggests that complement components and prostaglandins in particular be sought.[20]

Pharmacologic therapy for the carcinoid syndromes and for the tumors has been recently reviewed by Hill.[21] Though many agents have been employed, few are of any predictable and reproduceable value. The toxic side-effects of many of the drugs further limit their use. The investigators at the National Institutes of Health have had good experience with alpha-methyldopa (Aldomet) in managing the syndrome associated with gastric carcinoid tumors and with steroids in

A GRAPHIC ANALYSIS OF THE CLINICAL PRESENTATIONS OF CARCINOID TUMORS OF VARYING SITES

SYNDROME	PRIMARY SITE	DOMINANT SIDE OF ENDOCARDITIS	URINARY METABOLITE	COMMENTS
Classical	Small Intestine	Right	5-HIAA	Hepatic metastases present when syndrome appears.
Pelvic Variant	Ovary	Right	5-HIAA	Venous drainage directly into systemic circulation; syndrome occurs in absence of metastatic disease. Very rare.
Gastric Variant	Stomach	Right	Histamine	Flushing pattern unique and characteristic—frequently induced by eating. 5-HTP secreted by tumor but normal amount excreted in urine; 5-HIAA normal in urine. Usually associated with hepatic metastases; α-methyldopa of value by blocking 5-HTP conversion to serotonin.
Bronchial Variant	Tracheobronchial tree	Left	5-HIAA	Prolonged flushing with facial and periorbital edema, hypotension, oliguria. Other endocrine syndromes may be associated. Good symptomatic response to steroids.
Rectal Carcinoids	Rectum	—	—	Not associated with a carcinoid syndrome. Rarely spreads to local nodes.



Metabolic interconversion of tryptophan to 5-HIAA. The structures of niacin and histamine are presented.

managing the syndrome associated with bronchial carcinoids.[22,23] Specific antitumor therapy is lacking. Surgical intervention may be curative in bronchial and ovarian carcinoid tumors which are localized. Though not associated with a carcinoid syndrome, the malignant potential of rectal carcinoids has recently been emphasized and their removal should be encouraged.[24]

Malabsorption in Abdominal Lymphoma

Lymphomatous involvement of mesenteric lymph nodes and intramural lymphoid tissue occurs commonly in disseminated lymphomas. Despite this, malabsorption syndrome is an uncommon accompaniment of disseminated lymphomatous disease. This subject has been reviewed several times in recent years.[25–27] Less than one hundred reported cases have appeared in the literature since the first reports thirty-five years ago.[26]

In 1966, Eidelman and his coworkers reporting from Israel described a unique type of intestinal lymphoma which characteristically presents with malabsorption.[25] The nine patients these authors described were typically young, usually in the second and third decades of life. Steatorrhea, abdominal pain, abdominal masses, and clubbing of the fingers were commonly seen. Hepatosplenomegaly and peripheral lymphadenopathy were absent in these patients. The afflicted patients were non-European Jews and Arabs and the term "Mediterranean lymphoma" was applied to this entity. Subsequent cases have been reported from Italy, France, and in South African Blacks.[28–30] Two cases have recently been reported from the Western hemisphere.[31] A common denominator of the afflicted patients seems to be low socioeconomic status and a poor dietary history.

The gross and histopathologic features of this lymphoma are quite heterogenous.[25,30,31] Cellular infiltrates vary from dominantly plasma cells to lymphocytes to histiocytes.

The serum and urine of many of these patients contain a fragment of IgA. This fragment is apparently the Fc piece of the heavy chain of the α_1 subclass.[28,29,31] The term "alpha chain disease" has been applied to this entity, the third of the heavy chain diseases to be described.

A different clinical form of alpha chain disease has been described in a Dutch child with normal gastrointestinal function but with a premalignant hypopharyngeal paragranuloma and interstitial lung disease. The Fc fragment of the alpha heavy chain was present in the serum of this patient also.[32] That respiratory and gastrointestinal tract lymphoid neoplasms should be associated with disorders of IgA metabolism is not surprising since these organs are major sites of IgA production.[33]

Obstipation

Though commonly seen in chronically ill debilitated and bedridden patients, constipation can be an important clinical clue to the presence of hypercalcemia.

A glucagon-producing tumor arising in the kidney has been associated with alterations of small bowel morphology, motility, and absorptive function.[34] Profound obstipation with abdominal swelling and intermittent nausea and vomiting resulted in an exploratory laparotomy before the proper diagnosis was made. Removal of the renal tumor resulted in a brisk amelioration of symptoms.

Protein-Losing Enteropathy

Protein-losing enteropathies have been reported in association with esophageal, gastric, and intestinal carcinomas in addition to lymphomas.[35,36] Whether the loss takes place only through a disrupted epithelium overlying the neoplasm, or whether the malignancy includes protein loss through the entire length of the bowel remains a mystery.

Nonspecific Reactive Hepatitis

A syndrome resembling chronic hepatic dysfunction has been noted in a number of patients with hypernephroma.[37] The livers are frequently enlarged though non-tender and a number of liver tests are abnormal. Increased alkaline phos-

phatase activity, increased bromsulphalein (BSP) retention, elevated bilirubin, hypoprothrombinemia, hypoalbuminemia, and an elevated alpha-2 globulin are commonly seen in these patients. Biopsies of the liver reveal the changes of nonspecific reactive hepatitis in varying degrees of severity. This syndrome seems to be entirely reversible with successful removal of the hypernephroma.

MUSCULOSKELETAL MANIFESTATIONS OF NEOPLASIA

Gout may occur in predisposed patients with hyperuricemia associated with lymphoproliferative and myeloproliferative disorders. Rheumatic symptoms and the carpal tunnel syndrome are frequently seen in patients with amyloidosis associated with myeloma. A rheumatoid syndrome has been associated with prostatic cancer[38] and polymyalgia rheumatica may herald a malignant disease.[39] Arthritis occasionally resembling gout can occur with pancreatic neoplasms, frequently in association with subcutaneous fat necrosis or an erythema nodosum-like lesion.[40]

Clubbing (Acropachy)

"Clubbing is one of those phenomena with which we are all so familiar that we appear to know more about it than we really do."[41] That sixteen trained observers gave fourteen definitions for clubbing seems to verify this nineteenth century admonition.[42] The guidelines reviewed by Mendlowitz and by Fischer and his associates seemed to provide acceptable diagnostic criteria.[43,44] An increase of the angle (normal, about 160 degrees) between the soft tissues of the nail bed and the point where the nail emerges from the finger constitue an important diagnostic feature. This, however must be present in association with a softening and thickening of the soft tissues of the nail bed. This frequently allows increased mobility of the nail plate.

Clubbing may be either constitutional (familial or congenital) or acquired. The acquired form is more common and may be associated with hypertrophic osteoarthropathy. The majority of cases of acquired achropachy are not associated with neoplastic diseases. A variety of pulmonary, cardiac, gastrointestinal, hematologic, and hepatic illnesses have been associated with acquired clubbing.[43–45] When associated with a neoplasm, the clubbing is frequently painful and rapidly progressive. Virtually every sort of intrathoracic malignancy has been associated with clubbing. This includes carcinomas, teratomas, sarcomas, mesotheliomas, neurinomas, lymphomas, and Hodgkin's disease.[45] Though the pathogenesis of this syndrome remains obscure, remissions frequently follow tumor-directed therapy.

Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy is almost always associated with clubbing. It is best thought of as a proximal extension of the clubbing process. The acquired form is characterized by painful, warm swelling of the distal extremities with radiologic evidence of periosteal new bone formation. Clinical confusion with rheumatoid arthritis is common, and radiologic analysis is useful in elucidating the true diagnosis. Increased blood flow to the distal extremities has been demonstrated.[46] A familial variety of hypertrophic osteoarthropathy exists though the majority of cases are acquired and they are usually associated with bronchogenic carcinomas or intrathoracic mesotheliomas.

The pathogenesis of this syndrome remains obscure. Hypertrophic osteoarthropathy is frequently seen in association with gynecomastia. Ginsburg and Brown demonstrated increased estrogen excretion in eleven men with hypertrophic osteoarthropathy. The levels fell in the six patients in whom an intrathoracic tumor was successfully removed.[47] Greenburg and his associates, however, have recently demonstrated quite convincingly that a poorly differentiated carcinoma produced human growth hor-

mone in a patient with hypertrophic osteoarthropathy. Eight weeks after resection of this tumor, the clubbing and hypertrophic osteoarthropathy completely cleared.[48] In addition to the direct assaults on the tumor, simple thoracotomy or section of the vagus nerves either at the hilum or distant from the hilum has been associated with remission of hypertrophic osteoarthropathy.[41,49,50]

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THE USE OF FIBER METAL COMPOSITES AS A METHOD OF FIXATION OF SKELETAL PROSTHESIS

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INTRODUCTION

One of the problems encountered in the development of an internal prosthetic device is the fixation of the prosthetic components to the surrounding bone. Currently, internal prostheses are fixed to bone by one of three methods: 1) Internal fixation (e.g., screws), 2) impaction of the prosthetic stem into the medullary cavity of the bone, and 3) using a cement or filler (such as methyl-methacrylate) between the prosthesis and the bone.

Problems can arise with any one of these methods, and an alternative solution would be desirable. A possible method of firm fixation for a skeletal prosthetic device is through bone ingrowth into the void spaces and channels of a porous material.[1–10]

Although bone and connective tissue ingrowth are feasible with a variety of materials, certain specific requirements must be filled to provide a basis for fixation of a prosthetic device. Pore size is an important variable. The experiments of Hulbert and Klawitter have indicated that a minimum interconnecting pore size of 100μ was necessary to obtain bone invasion. In addition, the pore channels must be continuous. Porosities of this magnitude will result in materials that are structurally weak. That is to say, the stresses for failure by distortion or by fracture will be small. For that reason, the porous materials in most cases will be used in the prosthetic design as a thin layer bonded to the surface of the prosthesis where bone fixation is needed. This poses, in general, problems in manufacturing. Regardless of the method used control of external dimensions is quite often impossible. Clinically, this is a vital issue because bone invasion requires a very close conformity between the hole or cavity prepared and the prosthesis to be inserted.[8]

In addition to problems of manufacturing, there are serious considerations related to the mechanics of service. The superficial porous layer will experience the same distortions as the strong weight-bearing substrate. Unless the elastic modulus of the porous material is at least two orders of magnitude smaller than the load-bearing substrate, the stresses developed in the porous zone will likely

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exceed a failure limit. Consequently, to avoid failure the porous material must be very compliant: large deformations should result from relatively small stresses.

A large compliance in the porous material at the prosthesis bone interface will have an added advantage. It will prevent the occurrence of stress concentrations and subsequent local bone reabsorption serving as a load distributor in the interface.

The porous material must be crack-resistant, particularly under impact. Metallic or ceramic porous materials are usually manufactured by sintering powders. Porous ceramics are very weak and brittle; they tend to crack or shatter under small impact energies. Consolidated sintered metal powders with porosities in the range of 40-60 percent void are stronger, but are still brittle and have poor resistance to crack propagation. Both sintered metallic or ceramic powders are relatively poor compliant materials.

The considerations presented thus far lead to the choice of a porous aggregate produced from 316 L stainless steel, unalloyed titanium and Vitallium wire.

The metallic wire is cut in short lengths, kinked and molded into precise shapes using constraining dies and moving punches (Figs. 1 and 2). The choice of the wire size and the density will govern the final pore dimensions of the composite.

The molding operation is followed by a sintering stage in which points of contact between fibers become actual metallurgic bonds. Sintering programs of 1070-1240° C for two hours gave adequate bonding.

In a molded and sintered body produced from wire, the porosity is completely interconnecting. The pore shapes cannot be described in any simple geometrical terms (Fig. 3). The largest principal dimension of these pores is approximately equal to the wire diameter when the void content is about 50 percent. Obviously pressing to higher densities would lead to more constricted pore channels.

The elastic properties of this class of materials are more like an elastomer than like a metal. They exhibit a very low elastic modulus ($10^4 kg/cm^2$); this is a safeguard against high localized stresses and provides for a load-distributing behavior that reduces the possibilities of bone resorption.

A fiber metal sintered composite cannot fail by the propagation of cracks. Failure is by rupture of individual sintered bonds and is a progressive process involving total extensions of about 100 percent. Stresses of the order of 70-140 kg/cm^2 are reached during the tearing test in tension. Impact forces do not produce catastrophic failure. In Figure 5, a bar of sintered Vitallium wire has been impacted with a hammer blow in three-point bending. The distortion produced is far in excess of that which would have been tolerated by a solid center shaft of the same alloy. The damage produced was rupture of some of the sintered bonds.

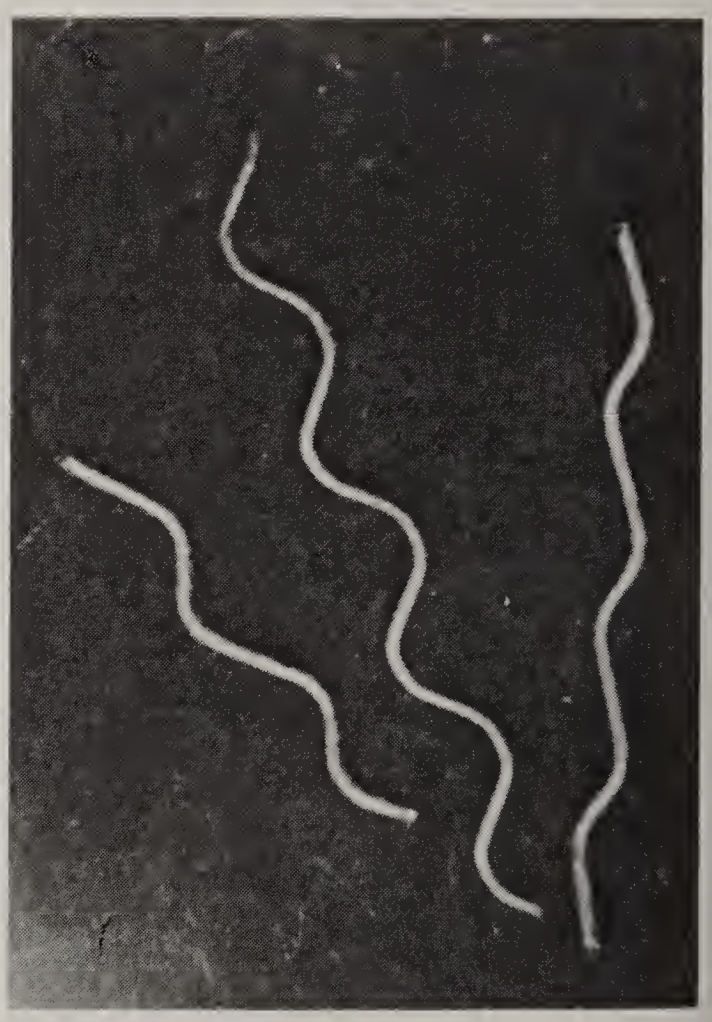

Fig. 1—A view of the cut lengths of wire as used for molding. The wire has been pre-kinked by passing through a set of meshing gears.

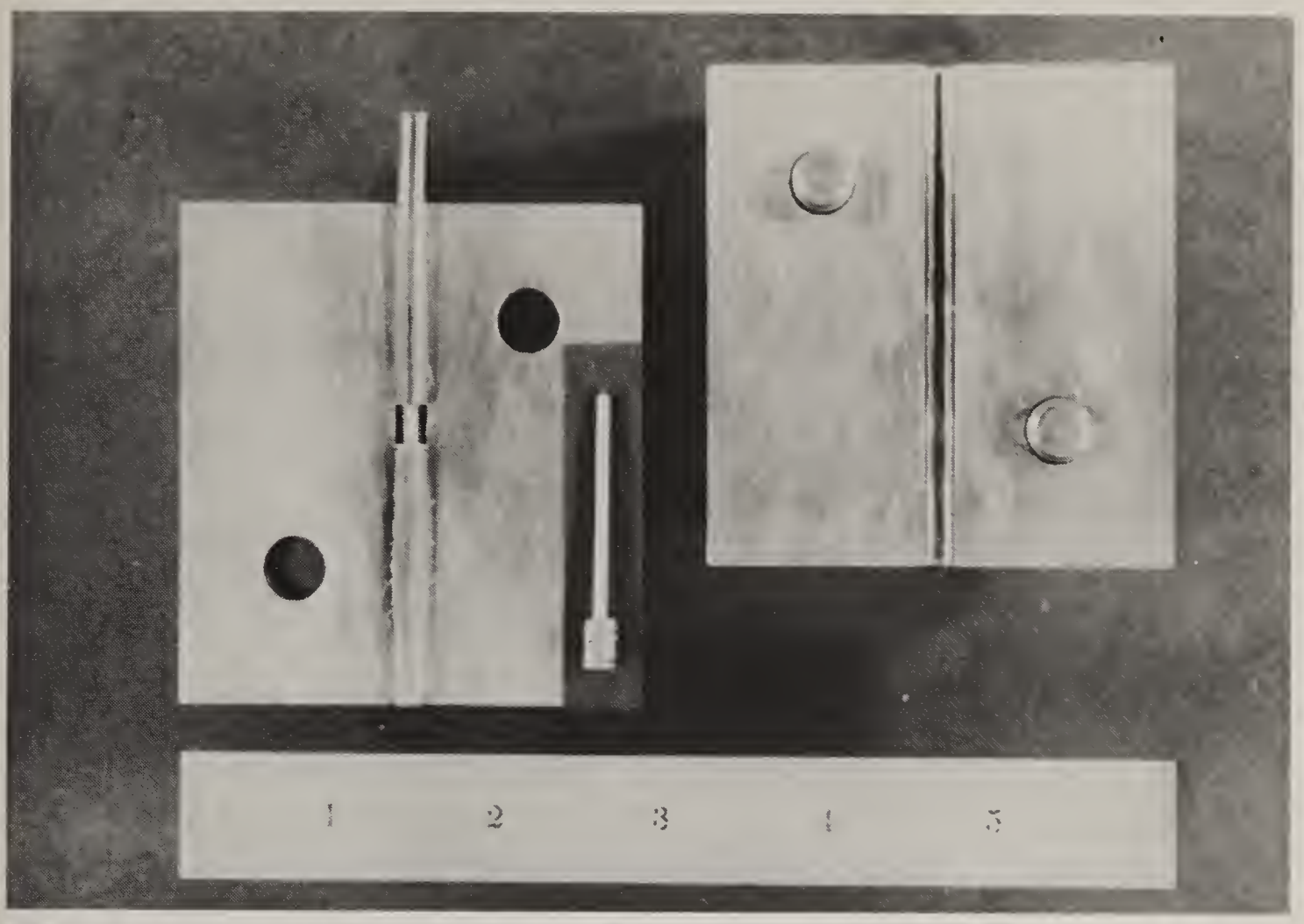

Fig. 2—Demounted view of a punch/die assembly for molding wire around a flat-head, nail-shaped, prosthesis that in composite is the model for a permanent, artificial tooth root. The upper punch moves and is a tubular element. (Scale in inches.)

Fig. 3—The appearance of a molded wire aggregate. Note particularly the non-specific geometry of the pores and the variation in principal dimensions.

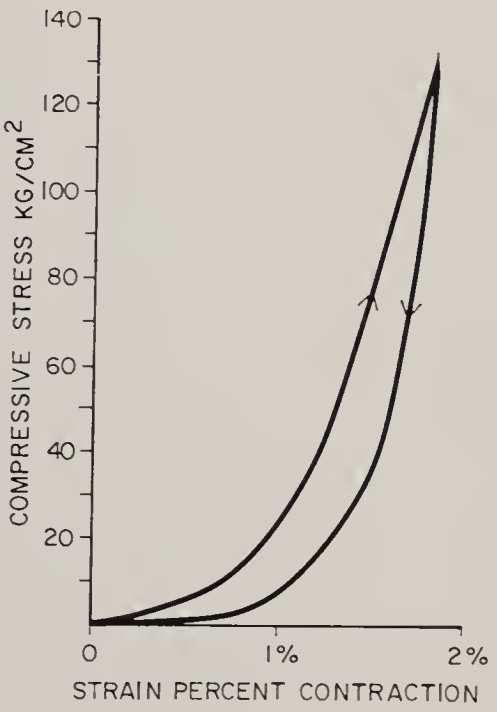

Fig. 4—Graphical representation of a reversible (elastic) stress-strain cycle. Material is Vitallium wire of 0.023 cm in diameter molded to 50 percent porosity and sintered at 1240°C. for three hours. Before testing, the sintered cylindrical specimen was recompressed to 7 percent reduction in height.

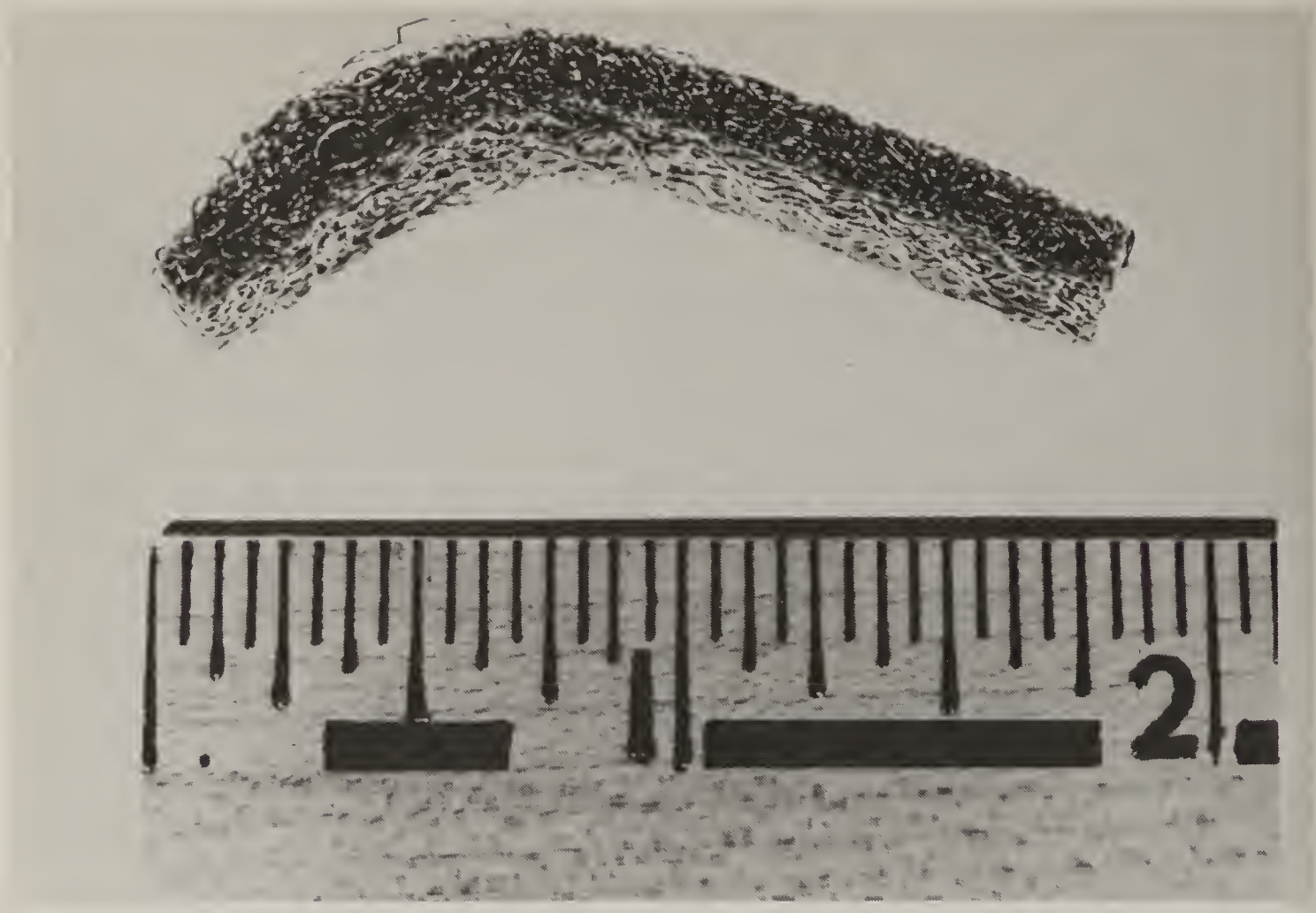

Fig. 5—Appearance of a bar molded from Vitallium wire of 0.009 in. in diameter to 60 percent porosity which has been subjected to a hammer blow in three-point bending. (Scale in inches.)

BONE INGROWTH

Initial studies of bone ingrowth have been performed in dogs and in rabbits. Titanium fibers were used for manufacturing these composites. Samples were inserted in the trochanteric and supracondylar regions of the femurs of the experimental animals and sacrifice and recovery was performed at progressive intervals up to 12 weeks following implantation. Undecalcified embedding and sectioning techniques were used for histological study. Within four days of implantation, blood cellular elements were seen within the framework of the implants. New bone formation was evident at 14 days in the periphery of the implants and after three weeks, bone ingrowth had occurred into the void spaces of the composites. Almost complete infiltration was observed within 12 weeks after implantation (Fig. 6). Intimate contact between implant and surrounding bone appeared to be essential to obtain bone ingrowth. Bone ingrowth in the rabbit was more massive than in the dog, and no rejection of the samples was obvious in any of the experiments.

THE STRENGTH OF THE BONE IMPLANT BOND

The strength of the bone implant bond was studied in implants performed in the femoral trochanteric regions of dogs. Cylindrical specimens made of titanium fibers 12.7 mm long by 9.52 mm wide were molded to 50 percent porosity. The fibers were molded around a threaded solid titanium rod 3.17 mm in diameter.

In subsequent tensile tests performed with an Instron testing machine, a fixture rod was threaded over the upper projection of the center rod to pull the specimens out from the bone. The force required to pull the specimens out from the bone was measured and the shear strength of the bone-specimen interface was calculated on the basis of the surface

area of the specimen. Shear strength increased from an average of 2.52 kg/cm² in the 24-hour specimens to values around 20kg/cm² after the second week where it remained constant up to three months following implantation. The maximum shear strength values correlated with the occurrence of peripheral bone formation and penetration of this bone into the surface pores of the implants. Deep penetration of bone did not increase the shear strength of the interface. Failure always occurred in the bony trabeculae at the prosthesis-bone interface.

In subsequent experiments, the effect of changes in pore size on bone ingrowth and on shear strength was studied. The results were compared to the strength of fixation obtained using methylmethacrylate. The specimens used were 9 mm in diameter by 50 mm long. The average pore size of the fiber metal composite was altered by using wire of varying diameter and compressing the samples to a uniform density. These samples were made using titanium fiber of 1.25, 1.88 and 3 mm diameter with a density of 50 percent. Average pore sizes were 190, 130 and 390μ respectively. Eighteen dogs were used in this experiment. Nine animals had fiber metal implants divided into three groups of three dogs each with three different types of fiber metal implants respectively. The animals were sacrificed six weeks postoperatively and the shear strength of the bone implant interface was obtained.

The specimens fixed with methylmethacrylate were threaded stainless steel shafts 63.5 mm in length by 6.4 mm in diameter. Nine dogs had implants of this type fixed with methylmethacrylate. In seven animals (14 femurs), sacrifice and testing of shear strength was done 48 hours following implantation. The remaining two dogs (four femurs) were sacrificed six weeks following the initial surgery.

The mean shear strength of fixation varied from 1.7 to 16.8 kg/m². No statistically significant differences were elicited between any of the groups. The fiber metal and the acrylic resulted in essentially the same strength of fixation after six weeks of bone ingrowth. Changes in pore size between 190-390μ did not influence the shear strength of the interface. Bone ingrowth was confirmed in all of the fiber metal samples. All of the incorporated bone was trabecular in nature. The 1.25 mm wire composite with smaller pores appeared to contain a large number of thin trabeculae whereas the 3 mm wire composite seemed to support wider trabeculae which were few in number.

More recently, another series of implants was performed in five animals (10 femurs). The implants were manufactured from Vitallium fiber composite 2 mm in diameter, incorporating a central Vitallium rod. Sacrifice, mechanical testing and histological study of the samples were performed as in the previous experiment, six weeks following implantation. Shear strength values and histological evidence of bone ingrowth were of the same nature as those obtained with titanium fiber metal composite.

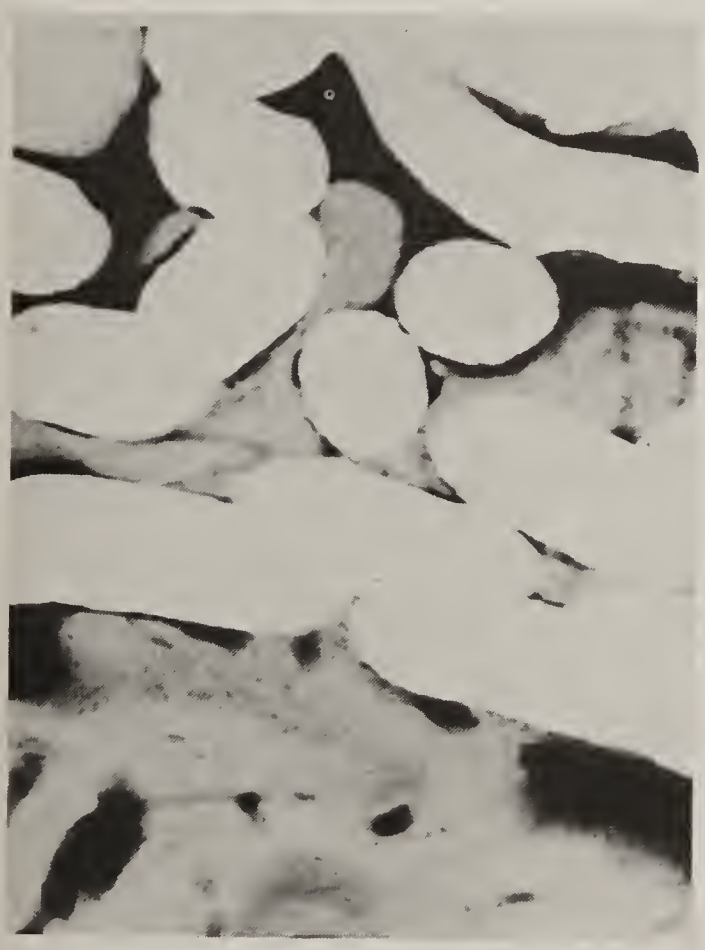

Fig. 6—Microradiograph of titanium fiber composite infiltrated with bone three months after implantation in dog's femur.

FEMORAL PROSTHESES

The ultimate test of a device for prosthetic fixation is success under the stresses of weight-bearing. A model experiment was designed in which femoral head prostheses were implanted into dogs. These prostheses incorporated a stainless steel femoral head and a shaft made of a central titanium rod over which was placed a square fiber metal sleeve using 1.88 mm titanium wire and a density of 50 percent. The square shaft provided temporary mechanical interlock with the bone following implantation until such time as bone ingrowth had occurred. The animals were sacrificed at three months, six months and one year following surgery. They appeared to walk bearing their full weight on the operated limb during the period of experimental observation. At autopsy, all the prosthetic implants were securely fixed in the femoral shaft. Transverse sections performed at four different levels revealed bone ingrowth into the fiber metal in every section. In the proximal end of the bone, where bony trabeculae were in contact with implant, the ingrowth was massive. In the distal end, where the femoral prostheses were contacting the endosteal surface of the cortical shaft, ingrowth was obvious only at the areas of contact of the square shaft with the cylindrical bone. In summary, weight-bearing up to one year did not affect the ingrowth of bone and maintenance of skeletal fixation in fiber titanium-coated femoral prostheses.

THE SKELETAL REPLACEMENT SEGMENT

The purpose of this experiment was to study the feasibility of replacing a major segment of a long bone in an adult primate. The possible clinical implications of this model relate to situations where major loss of bone segments occurs secondary to trauma or to primary bone tumor where the surgeon might elect to do a massive resection rather than amputation of the limb. A replacement of the 7.5 cm of the femoral shaft of the adult baboon was designed.

The implant (Fig. 7) consisted of a

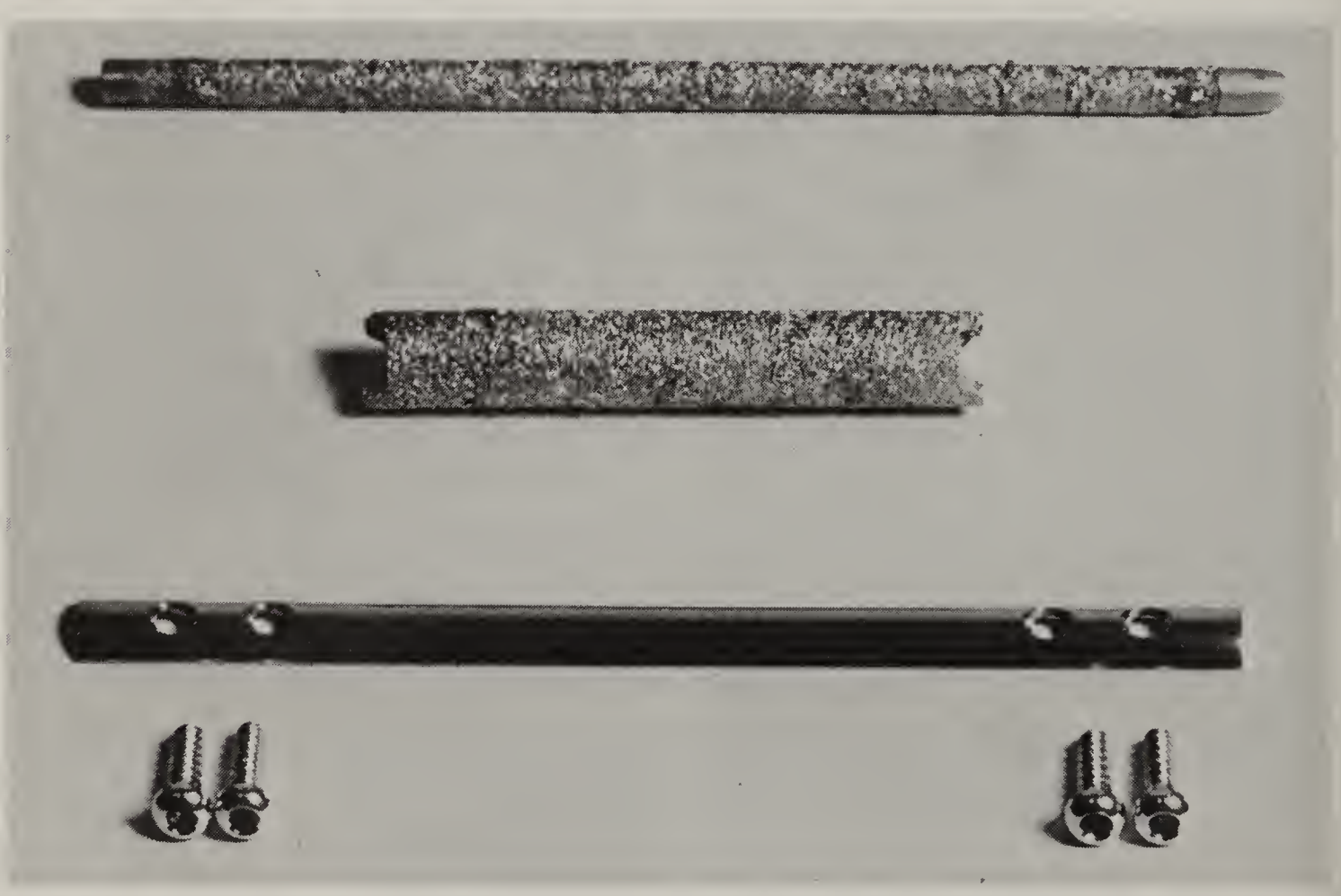

Fig. 7—Segmental bone replacement for a baboon's femur.

fiber titanium central section to replace the excised cortical segment. Fixation was provided by 1 cm long flanges at both ends of the replacement segment to be fitted into notches created in the remaining femoral cortices. A central intramedullary stem with a rigid Ti 6 percent Al 4 percent V core and a fiber titanium coating on the surface fitted right into the intramedullary cavity of the bone and through the center of the prosthetic intermediary segment. A semi-tubular plate was then attached to both the proximal and distal femoral cortices with two screws above and two below to provide added stability.

Implantation has been performed in eight animals. The longest follow-up interval in this group is eight months. Callus formation surrounding the intermediary replacement segment has been observed from the second week following implantation. Figure 8 illustrates the amount of new bone formation typically observed 10 weeks following implantation. All animals are ambulating at the present time without an obvious limp. In summary, incorporation of the porous intermediary segment and ingrowth of bone leading to a stable extremity appear to have occurred in all of the animals.

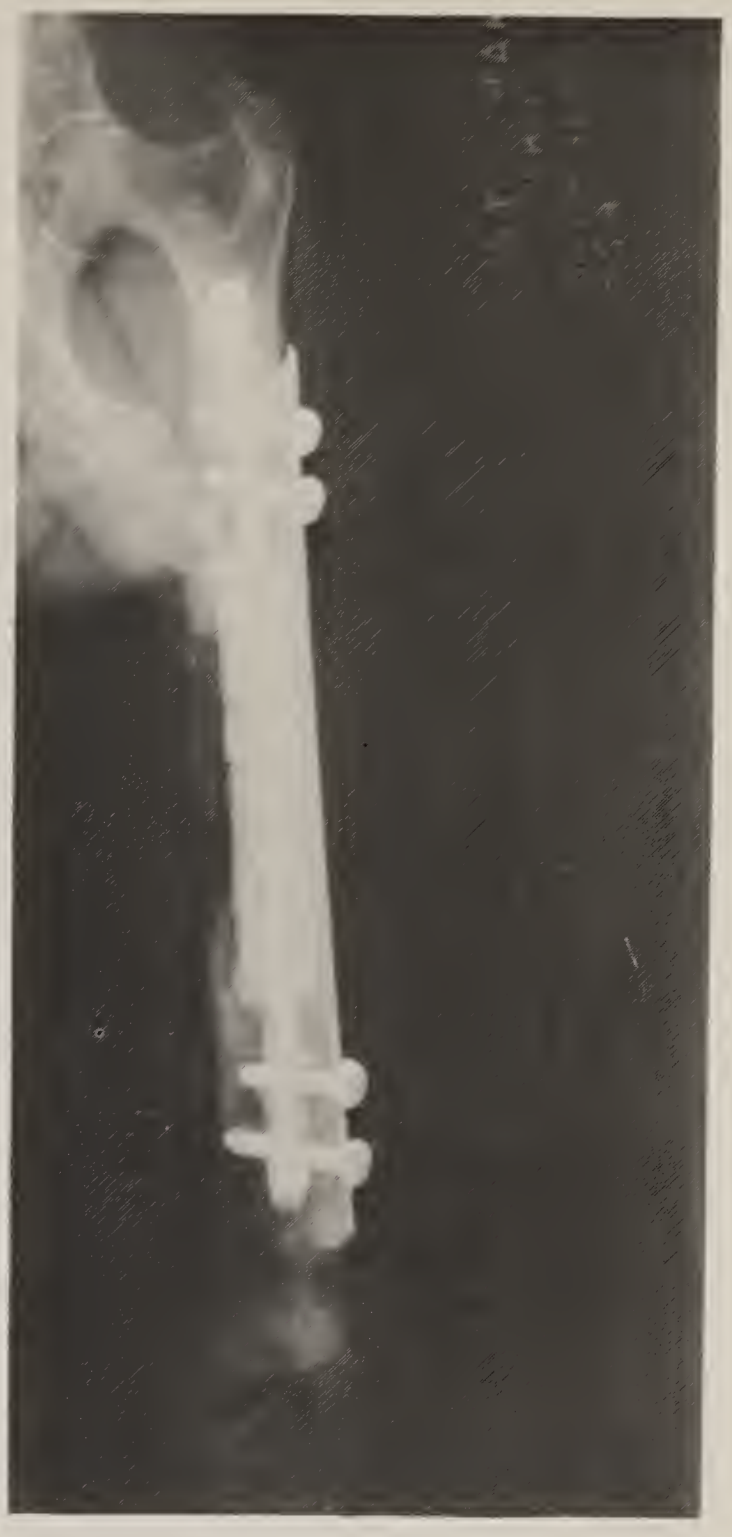

Fig. 8—Segmental replacement in a baboon 10 weeks after implantation showing bone formation on the medial side of the implant.

DISCUSSION

The experimental evidence thus far obtained indicates that fiber metal composites can be very successful in the fixation of skeletal prostheses. There are some problems, however, that relate to its use, both from a technical and a biological viewpoint.

From a surgical viewpoint, the use of fiber metal presents considerably more technical difficulties than the use of methylmethacrylate. The technique of insertion of a prosthesis incorporating fiber metal must be exacting to provide intimate contact between metal and bone and at the same time, temporarily prevent motion until bone ingrowth has occurred. Methylmethacrylate achieves its strength at the time of surgery and even though the fixation obtained with fiber metal may have reached its maximum strength as early as three weeks, it does not have the advantage of the immediate bonding available with a self-curing acrylic. There are clinical situations, such as the rheumatoid patient under steroid therapy, where the phenomena of bone ingrowth may not occur to any satisfactory degree.

There is no acute toxicity when an implant is composed entirely of inert metal. However, the surface area of the fiber metal implant was calculated to be 18 times larger than that of a solid im-

plant of the same size. Corrosion products from such a large surface area may have long-term toxic effects that are at the present time unknown and are under investigation in our laboratory.

A prosthesis incorporating fiber metal composites in its surface must be made failure-free. Removal of such devices infiltrated with bone would present an extremely difficult, if not an impossible surgical problem. A failure-free device is, however, not feasible given the current state of the art, and this is perhaps one of the greatest deterrents to the clinical use of this material at present.

SUMMARY

Fiber metal composites of special porous design have been shown to fix skeletal prostheses firmly after implantation, by ingrowth of cortical bone. There has been no acute toxicity or rejection in numerous experiments. Problems still to be solved include: surgical technical difficulties of installation; the possibility of long-term corrosion and toxicity; and the extreme difficulty, if not impossibility, of removing a failed device.

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FAMILIAL MEDULLARY CARCINOMA AND PARATHYROID ADENOMA WITHOUT PHEOCHROMOCYTOMA: REPORT OF TWO CASES

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Will G. Ryan
Steven G. Economou
Glen W. Sizemore
Claude D. Arnaud

INTRODUCTION

The association of medullary carcinoma of the thyroid gland, pheochromocytoma, hyperparathyroidism, and Cushing's syndrome, in various combinations, an entity designated as multiple endocrine neoplasia, Type II, has recently been well described.[1] It is familial, and the inheritance is compatible with transmission through an autosomal dominant gene.[1] However, the association of medullary carcinoma and parathyroid adenomas without pheochromocytoma is unusual, only two cases having been reported in the literature. This report describes a family of four siblings, three with medullary carcinoma of the thyroid, two of whom had associated parathyroid adenomas. As yet, none has detectable evidence of pheochromocytoma. The two siblings with parathyroid adenomas presented with hypercalcemia and renal stones.

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Studies of serum calcitonin, a polypeptide secreted by parafollicular cells of the thyroid, previously shown by others[4, 5] to be elevated in patients with medullary carcinoma, are also presented. The assay for serum thyrocalcitonin has been described previously.[5]

REPORT OF CASES

Case 1: W. B. (PSLH #1891051), a 30-year-old white male was well until six months prior to admission when he suffered an episode of renal colic. At that time he was found to have elevated serum and urinary calcium. Two months later, in January 1969, he underwent a neck exploration at another hospital and was found to have had two "parathyroid adenomas" embedded in the right lobe

of the thyroid gland. A right hemi-thyroidectomy with removal of the two "adenomas" was performed, but serum Ca remained elevated postoperatively, despite a low calcium diet. He was admitted to Presbyterian-St. Luke's Hospital on April 18, 1969, with a history of leg-muscle soreness, generalized fatigue, and frequent urination. He was taking no medicines. The blood pressure was 130/90. The neck had a low transverse scar, and the thyroid was not palpable. There was no lymphadenopathy. The remainder of the physical examination was within normal limits. On admission, hemogram and urinalysis were normal. The Na was 144 mEq/L, K+ 4.3 mEq/L, CL 104.0 mEq/L, CO_2 29.6 mEq/L, Ca 11.1 mgm per 100 ml (Normal, 8.7 to 10.7 mgm per 100 ml), P 2.7 mgm per 100 ml (Normal, 2.5 to 4.8 mgm per 100 ml), Cr 0.9, Uric acid 7.3, PBI 5,0, and Murphy-Pattee T_4 5.4 μgm per 100 ml (Normal 3 to 7 μgm per 100 ml). The serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), alkaline phosphatase, and cholesterol were normal. The serum protein electrophoresis was normal. Urinary calcium excretion was 115 mgm, and phosphorus 0.61 gm/24 hours. Urinary 17-hydroxycorticosteroid (HCS) excretion was 21.3 and 17-Keto-steroids 11.9 mgm/24 hours. Radiographs of the chest, mandible, teeth, hands, and clavicles were normal. A bone biopsy showed increased osteoclastic activity consistent with hyperparathyroidism. On April 25, 1969, the patient underwent a second neck exploration, at which a left inferior parathyroid adenoma was excised. The patient was normocalcemic following surgery.

In May, 1969, a review of the histologic slides of his thyroid from the subtotal thyroidectomy in January, 1969 resulted in the diagnosis of medullary carcinoma of the thyroid. On May 12, 1969, his plasma thyrocalcitonin (CT) was drawn. It was reported later to be 222 pgm/ml (normal <500 pgm/ml). The 24-hour urine vanilyl-mandelic acid (VMA) was normal at 6.4 mgm/24 hours (Normal 0.5 to 8.6 mgm/24 hrs), and the serum parathyroid hormone level (PTH) was 14 μlEq/ml (normal ≤45 μlEq/ml).

Because of the new diagnosis, he was readmitted and, on June 23, 1969, the remainder of his thyroid gland was removed. No evidence of residual carcinoma was found in the specimen. Postoperatively his serum calcium and VMA have remained normal but he has continued to complain of vague gastrointestinal symptoms. In January, 1971, the serum CT was 319 pg/ml and the serum PTH was 38 μl Eq/ml.

Case 2: E.B. (PSLH #895249), a 33-year-old white male, was first seen in May, 1969, with history of kidney stones in 1964 and 1966, and bone pain and fatigue since childhood. He also had an eight-year history of diverticulosis which was exacerbated intermittently despite a low roughage diet. The patient took a phenobarbital-belladonna preparation for his bowel symptoms. Past medical history and a review of symptoms were negative. On physical examination his blood pressure was 130/80, the thyroid gland was two times normal size and slightly nodular. There was no lymphadenopathy, and the remainder of the physical examination was normal. Laboratory data showed a hemoglobin of 16.4 gm per 100 ml and WBC 8,000/mm^3. The urinalysis was normal. Serum electrolytes were normal. The serum calcium was 12.5, phosphorus 2.7, FBS 88, BUN 15, Cr. 1.3 and uric acid 8.6 mgm per 100 ml. He had a normal SGOT, bilirubin, alkaline phosphatase, cholesterol and serum protein electrophoresis. The PBI was 7.3 μgm percent and the Murphy-Pattee thyroxine was 6.5 μgm per 100 ml. X-rays of the chest, hands, clavicles, and skull were normal. Urinary 17OHCS were 6.6; 17-KS, 6.3; and VMA, 7.8 mgm/24 hrs. Urinary catecholamines were 68 mcgm/24 hrs. The qualitative test for urinary 5-HIAA was negative. A glucagon provocative test for pheochromocytoma was negative.

Table I shows the results of a calcium infusion test done preoperatively. Elemental calcium 4 mgm/Kg/hr in the

TABLE I

RESULTS OF PRE-OPERATIVE CALCIUM INFUSION TEST

	Ca (mgm/100 ml)	P (mgm/100 ml)	Calcitonin (ng/ml)*
BASAL	12.9	2.4	6.4
1 hour	13.5	2.6	17.4
2 hour	14.3	3.0	23.4
3 hour	14.8	3.0	23.0
4 hour	15.2	3.3	22.8

*By radioimmunoassay — normal < 0.5 ng/ml.

form of calcium gluconate was infused over four hours.

On June 2, 1969, a total thyroidectomy and removal of a solitary parathyroid adenoma was done. The left lobe of the thyroid gland was found to have multicentric medullary carcinoma; the parathyroid adenoma was adjacent to the left upper pole of the thyroid. The postoperative course was uneventful, and the patient has done well on thyroid extract since discharge. In March 1970, his plasma calcitonin was less than 100 pgm/ml and his serum calcium was 10.2 mgm per 100 ml. The serum PTH was 21 μlEq/ml. In February 1971, the CT was <100 pgm/ml and PTH 10 μlEq/ml.

Case 3: K.M. (PSLH #907482), a 25-year-old white female, and sister of W.B. and E.B. underwent a subtotal thyroidectomy at age 18 because of a mass in the left thyroid, which did not regress with thyroid extract suppression. The pathologic diagnosis was follicular carcinoma of the thyroid gland. She was seen for the first time at Presbyterian-St. Luke's Hospital in August 1969 because of a right-sided mass in her thyroid gland 3 cm in diameter and the positive family history of medullary carcinoma. Past medical history was otherwise negative except for the previous thyroid surgery, and the removal of a fibro-adenoma in her right breast in 1967. Physical examination was otherwise normal. The hemogram and urinalysis were normal. The serum Ca was 10.3 and P 4.6 mgm per 100 ml. Urinary catecholamine excretion was 56 mcgm/24 hrs and VMA was 7.6 mgm/24 hrs. An I^{131} scan of the thyroid showed a normal right lobe. Table II shows the results of an intravenous glucagon injection (one mgm) given as a stimulus for calcitonin release.

On September 8, 1969, the patient underwent total thyroidectomy. Extensive tumor was present bilaterally with abundant disease involving the left cervical chain. A left cervical node dissection was performed. Only one parathyroid gland was identified and this was left intact. Microscopic examination of the

TABLE II

RESULTS OF INTRAVENOUS GLUCAGON (ONE MGM) INJECTION GIVEN AS STIMULUS FOR CALCITONIN RELEASE

	Ca (mgm/100 ml)	P (mgm/100 ml)	Calcitonin (ng/ml)*
BASAL	10.3	4.6	8.5
5 min.	—	—	16.4
10 min.	10.3	3.6	10.9
20 min.	10.2	3.6	5.45 (hemolyzed)
40 min.	11.0	3.6	6.95
60 min.	9.8	3.8	6.5

*By radioimmunoassay — normal < 0.5 ng/ml.

surgical specimen showed medullary carcinoma of the thyroid.

Postoperatively the patient has done well taking thyroid extract. However in June 1970, her plasma calcitonin was 3.6 ngm/ml, indicating a residual tumor. Her serum PTH was 9 μlEq/ml. (But in December 1970, her plasma CT was 8.6 pgm/ml and the PTH 21 μlEq/ml.)

Case 4: D.C., a 32-year-old white female, is the fourth sibling. She has had no previous medical illnesses and is normal on physical examination. In June 1969, her serum Ca was 10.0 and PO_4 2.8 mgm per 100 ml. A 24-hour collection of urine had normal catecholamines, and VMA and the serum calcitonin level was normal at 165 pg/ml.

The I^{131} thyroid scan and uptake were normal. In June 1970, plasma calcitonin was 165 pgm/ml and PTH 24 μlEq/ml, in January 1970, the CT was <100 pgm/ml and the serum PTH was 24.0 μlEq/ml. In February 1972 a calcium infusion was performed without significant increase in serum calcitonin levels.

In addition to the siblings, their father reportedly died of cancer of the thyroid gland with metastases to the lumbar vertebrae. As yet none of the siblings has demonstrated evidence of having a pheochromocytoma. However, their paternal grandfather reportedly died at the age of 35 while "Indian wrestling," this perhaps being suggestive of the presence of pheochromocytoma. In January 1971, the two children of D.C., Case 4, had normal CT and PTH values. W.B. and E.B. have no children. K.M.'s children are as yet considered too young for serum calcitonin examination. More remote family members have been unavailable for examination.

DISCUSSION

As noted in the introduction, the combination of medullary carcinoma of the thyroid and parathyroid adenoma without pheochromocytoma is quite unusual. The two patients reported here bring the reported cases to a total of four. The combination of medullary carcinoma, parathyroid hyperplasia or adenoma, and pheochromocytoma, however, has been reported in ten patients,[1,6,7] six of these having parathyroid adenomas.[7–11]

During the past decade calcitonin has been well characterized and its origin and mechanisms of action elucidated.[12] Meyer and Abdel Bari[13] demonstrated that calcitonin is formed in neoplastic cells of the parafollicular type seen in medullary carcinoma of the thyroid, and plasma from patients with medullary carcinoma has shown calcitonin-like activity in rats. The radioimmunoassay for calcitonin[5–14] can now be efficaciously used clinically to detect and follow patients with medullary carcinoma. The results obtained in our patients demonstrated this well. W. B., who had had a previous partial thyroidectomy in which medullary carcinoma was removed had a normal calcitonin level, although this was not known until later. On re-exploration to remove the remainder of the gland, there was no residual tumor in the surgical specimen. E. B. had elevated levels of calcitonin pre-operatively which fell to normal with total thyroidectomy in which medullary carcinoma was found. K. M. who had had previous surgery and metastatic disease in lymph nodes, had elevated levels both pre- and post-operatively, indicating residual carcinoma. Despite the finding of normal levels of calcitonin in W. B., total thyroidectomy was still indicated since the parafollicular cells in the remaining thyroid may have the potential for malignancy.

Both calcium and glucagon infusions have been used as stimuli for calcitonin release. In one of our patients glucagon caused an early two-fold increase. In another patient a calcium infusion caused an approximately four-fold increase which was sustained throughout the period of infusion. Increases in calcitonin levels with calcium infusions have been seen in normal patients but with less marked response. There have been conflicting data with respect to an increased secretion of calcitonin in response to glucagon, especially in malignant parafollicular cells.[5,16]

It is of some interest to speculate on the reasons for co-existence of a calci-

tonin-secreting tumor and parathyroid hormone-secreting tumor in the same patient. However, normal parathyroid hormone values in the presence of elevated thyrocalcitonin preclude a direct casual relationship. In addition, the frequency of other tumors associated with medullary carcinoma of the thyroid as a familial occurrence points to a genetic basis.

Because our patients had total thyroidectomy they have been maintained on replacement thyroid extract. Wahner, et al. have reported the regression of metastatic medullary carcinoma in one patient with TSH suppressive does of triiodothyronine.[16] The reason for this is not readily apparent as calcitonin would not be expected to be under control of TSH.

Recently Jackson[6] and Melvin[14] have reported on the diagnostic dependability of calcitonin assay in family studies for medullary thyroid carcinoma. We are currently examining the children of our patients for possible subclinical disease by this method as they do not have palpable abnormalities in the thyroid. Monitoring these subjects for possible future development of pheochromocytoma, as well as recurrent parathyroid adenomas is also indicated.

SUMMARY

Three siblings with medullary cancer of the thyroid without pheochromocytomas are presented. Of these, two had associated parathyroid adenomas and presented with hypercalcemia and renal stones. Only two other such patients are recorded in the literature.

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ELIE de CYON: HISTORICAL NOTE ON A PIONEERING MEDICAL PHYSIOLOGIST

Anatoly Bezkorovainy

"The history of science is an aid in scientific research. It places the student in the current of scientific thought, and gives him a clue to the purpose and the necessity of the theories he is required to master. It presents science as a constant pursuit of truth, rather than the formulation of truth long since revealed; it shows science as progressive rather than fixed; dynamic rather than static, a growth to which each may contribute. It does not paralyze the self activity of youth by the record of an infallible past . . ."

So wrote a distinguished scientific historian, a half century ago.[1] The only additional comments one could make, in terms of the reality of the 1970's, is that a study of the history of science and medicine is a highly satisfying endeavor which does not demand huge government grants or sophisticated laboratory facilities, and hence, costs almost nothing save for the investigator's time. The only requirement, which can be met by any medium-sized medical or educational institution, is the availability of a decent library. The Rush Medical School library is, for instance, quite satisfactory for such purposes.

Elie de Cyon has been almost totally ignored by modern scientific and medical historians because of the overshadowing stature of many of his contemporaries, such as Du Bois-Raymond, Ludwig, and Claude Bernard. Contemporary historians of Cyon's native Russia scarcely ever make any mention of him because Cyon held supposedly "reactionary" political views. He was truly of international orientation, having worked in the laboratories of Russia, France, Germany, and Switzerland. His skill as physiologic operator was, at that time, one of the best in the world, and this talent of Cyon's was repeatedly commented upon by his student at the Military-Medical Academy (St. Petersburg, now Leningrad), I. P. Pavlov, the Nobel laureate and father of conditioned reflex doctrines. It would thus be of interest to examine the life and contributions of this outstanding scientist so that he may eventually take his rightful place in the annals of the history of science and medicine.

Cyon was born in Samara (now Kuibyshev), Russia, on March 25, 1843, in a Jewish family. He received his education in Berlin, Germany, probably because of the limited educational opportunities in the Russia of that time. (As late as in 1897, there were only 10 universities with 15,000 students in Russia.) In 1866, we already find him working in Ludwig's laboratory in Leipzig, as a full-fledged research associate. The following year, he worked in Claude Bernard's laboratory, then returned to Russia in 1870 to accept a faculty position at St. Petersburg University. In 1872, Cyon was appointed to the chair of physiology at the Military-Medical Academy, in St. Petersburg, that had

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been vacated by Sechenov. He completely reorganized the method of teaching physiology at the Academy from a largely theoretical subject as presented by Sechenov to a practical course with many demonstrations and student participation. Cyon was knighted by Tsar Alexander II in recognition of his services and accomplishments. Cyon was apparently very proud of this, for thereafter he always used the titular prefix *de* or *von* with his name, depending on whether he published in French or German periodicals.

Cyon's political views were staunchly monarchistic (some say he was a "reactionary"), and hence, were extremely unpopular with his more leftist students. On many occasions, policemen had to be posted in the classroom to permit Cyon to lecture without interruption. Student harrassment finally resulted in Cyon's resignation and emigration to France. However, even there, the most liberal and egalitarian country on earth at that time, Cyon was unable to procure a position in a university because of his views. He then settled to book writing and politics. Having been appointed an agent to the Russian minister of finance, Cyon helped to procure French loans for Russia, and was thus instrumental in establishing the Franco-Russian alliance that became activated during the First World War. He died in 1912 without returning to Russia.[2]

Cyon can be described as primarily a cardiovascular physiologist.[3] He was a proponent of the nerve theory of heart action, as opposed to the then-popular myogen theory, and got himself into many arguments with the adherents to the latter. While working in Ludwig's laboratory in Leipzig in 1866, Cyon developed an apparatus for maintaining the circulation through a beating frog's heart. This permitted him to do numerous experiments on the effects of various stimuli and inhibitors of heart action.

The relationship between the heart rate and intensity of contractions was investigated by Cyon by varying the temperature at which the frog heart was perfused with fluid. He found that the intensity of the contractions remained at maximum from about 6 to 20°C, then decreased steadily until no contractions were noted at 37 to 40°C. The rate of heartbeat, on the other hand, showed a very slow rise between 6 and 20°C, then rose sharply to a maximum near 30°C, and then dropped to 0 at 37 to 40°C. From these experiments, Cyon postulated a law which states that the work capacity of the heart is constant and independent of temperature, and independent of the frequency of contractions.

With his brother, Cyon discovered the sympathetic *nervi acceleratorii* that arise in the lower cervical and upper thoracic ganglia and lead to the cardiac plexus. Their function was basically to counteract the action of the *vagi*: stimulation of *nervi acceleratorii* increased the frequency of contractions, but decreased their intensity. The Cyon brothers also discovered that the splanchnic nerves were powerful vasoconstrictors. Their resection caused a drop in the blood pressure of the animal, whereas their stimulation caused a rise in blood pressure. If the splanchnics were cut, the Cyons reasoned, then any fluctuations in blood pressure could be ascribed to the action of the heart. The brothers then stimulated the spinal cord of animals with severed splanchnic nerves and observed that the heart rate increased without an increase in blood pressure. They ascribed this effect to the accelerator nerves.

While working in Ludwig's laboratory, Cyon also discovered what he called *nervus depressor*. It later became known as the aortic presso-receptor nerve. Cyon found that this nerve originated in the neck region of the vagus and the superior laryngeal nerves, ran parallel to the sympathetic trunk, anastomosed with the inferior cervical ganglion, and then separated into numerous branches that innervated the heart. If the nerve was cut and the peripheral end stimulated, no effect was seen. If the central end of the cut nerve was stimulated, the heart rate decreased and the blood pressure dropped. Cyon, therefore, proposed that

this nerve had a sensory function. Cutting of the splanchnics completely abolished the blood pressure-lowering action of the *nervus depressor*. Cyon thus concluded that the nerve was connected with the vagus and the sympathetic centers of the brain, and served as a control device to protect the heart against overwork: as soon as the heartbeat would get too rapid, *nervus depressor* would be stimulated and would transmit its message to the splanchnic and vagal centers of the brain. The splanchnics would be inhibited, thus promoting vasodilation and a drop in blood pressure, whereas vagal signals would slow down the rate of heartbeat.

While working in Claude Bernard's laboratory, Cyon perfused frog hearts with fluids containing O_2, CO_2, and N_2. The heart required O_2 to keep beating, but CO_2 and N_2 caused it to stop. Cyon ascribed the effects of both temperature and the gases upon the heart as dependent on nerve stimulation or inhibition. He felt that a slow rise in temperature caused a stimulation of the *nervi acceleratorii* and a depression of the *nervus depressor*, and *vice versa* with decreasing temperatures. A sudden rise in temperature from 0 to 40 °C produced tetanus of the heart, and this was explained on the basis of a complete inhibition of the depressor nerve and a stimulation of the accelerating nerve. Cyon also proposed that the *nervus depressor* was responsible for the transmission of emotional stimuli from the brain to the heart.

Cyon was much interested in the physiology of space and time perception, and its relationship to the semicircular canals.[4] He damaged the latter in animals and divided the effects observed into three categories: (1) loss of equilibrium, (2) forceful movement immediately after the operation, and (3) dropping the head to the floor and erratic movements (three to four days after the operation). He then postulated that the semicircular canals were responsible for the perception in three dimensions, each of the three canals being responsible for one dimension. He noted that the lamprey with its two semicircular canals was able to move in only two dimensions, whereas the movements of the Japanese dancing mice (Tanzmäusen) with their single semicircular canal were only in a circular (one-dimensional) pattern. Of the two branches of the acoustic nerve, *nervus cochlearis* was found to be responsible for hearing, whereas *nervus vestibularis* was involved in space perception. The latter was found also to be connected with the eye, thus providing a connection of visual perception with the equilibrium centers in the semicircular canals.

De Cyon also tried his hand at the field of endocrinology, though he was somewhat less successful in this area than in cardiovascular physiology. He was, of course, handicapped by the fact that the concept of hormones and endocrine glands had not yet been formulated, hence his theories on the function of the thyroid and pituitary glands now seem to be quite amusing. He did most of his endocrinological work during his temporary association with a laboratory in Bern, Switzerland after his emigration from Russia.

Cyon felt that the thyroid gland had essentially two functions, one mechanical and the other biochemical.[5] In his extensive anatomical studies of the thyroid gland, Cyon discovered its extensive innervation and connection with the *vagi*. The purpose of such innervation, in Cyon's view, was to dilate the blood vessels of the thyroid, which indeed showed a remarkably high capacity to expand. This property of the thyroid gland vessels, Cyon felt, was to shunt large quantities of blood away from the brain in case the blood pressure got too high. This then served to protect the individual from strokes.

Cyon's view of the biochemical function of the thyroid gland was in the role of an iodine-trapping device and, at the same time, as a site of thyroxine synthesis. Thyroxine, Cyon found, was a valuable co-factor in the regulation of heart function and vasomotor activity by the *vagi*, where the thyroxine served to stimulate both the *vagi* and the depressor nerves to lower the frequency of

heartbeat, to increase the force of the contraction, and to cause a lowering of the blood pressure. Iodide, on the other hand, was a thyroxine antagonist, and had an inhibitory effect upon the *vagus*. He noted that the thyroidectomized animals showed the same symptoms as animals poisoned by NaI. Cyon felt that the thyroproteins were not toxic as had been previously proposed by Notkin[6], and represented merely a stage that was intermediate between iodide and thyroxine (this view was entirely correct). In collaboration with A. Ostwald, Cyon showed the non-toxic nature of thyroglobulins by injecting both the iodinated and non-iodinated thyroglobulins into experimental animals.[7] Only the iodinated thyroglobulins showed a depression of the blood pressure and a lowering of the heart rate. It was concluded that thyroxine was the physiologically active substance.

The function of the pituitary glands was also studied by Cyon during his visit to Switzerland.[8] He made pituitary gland extracts and injected them into dogs obtaining a small rise in the blood pressure, a decline in the frequency of heartbeat, and an increase in the strength of cardiac contractions. He assumed that the extract had stimulated the *vagi*, since the hypophysis extract, like thyroxine, was able to negate the effects of atropine on the nerves. Electrical or mechanical stimulation of the hypophysis gave similar results. Hypophysectomy resulted in an accelerated heart rate, an effect seen by cutting the *vagi*. Having, in his mind, established the relationship between the *vagi* and hypophysis, Cyon formulated a theory to the effect that hypophysis was capable of sensing increases in the intracranial pressure.[9] When such pressure became higher than normal, the hypophysis was stimulated mechanically, resulting in the stimulation of the *vagi*. This, in turn, resulted in a dilation of the thyroid gland veins and a constriction of arterioles. The blood pressure was thus increased, however, the blood flow was supposedly shunted through the thyroid thus relieving the brain pressure. In Cyon's view, the role of the pituitary was thus primarily a pressure-sensing device for the protection of the brain. The chemical (hormonal) function of the structure was merely a backup system for its mechanical function. Cyon's proposals on the function of the endocrine glands were thus primitive and in most cases erroneous. However, his work, carried out with precision and technical perfection, undoubtedly served as an important stimulus for further research in the area of endocrinology especially since Cyon was one of the first to propose the interrelationship between hypophysis and other internal secretion organs.

The adrenal gland did not escape Cyon's attention[10]. He found that the blood pressure was increased after the injection of adrenal extract, which was brought about because of a massive vasoconstriction. As in the case of the thyroid and the hypophysis, Cyon felt that these effects were entirely due to the action of the vagal and depressor nerves: adrenal extracts merely served to depress the activity of these nerves, since their stimulation could not bring about a reversal of the effects of adrenal extracts. On the other hand, adrenal extracts served to stimulate the accelerator nerves and, of course, the sympathetics. He also noted a momentary decline in the heart rate right after injecting the adrenal extract, and felt that this was due to the response of the hypophysis to the increased blood pressure in the cranial cavity.

In addition to his laboratory investigation, Cyon was a prolific writer, being the author of some 14 books in the Russian, German, and French languages. His greatest accomplishment in this field was the "Methodik der physiologischen Experimente und Vivisektionen" (1876), a manual of physiological experimental methods written both in German and Russian. It served as a standard physiological teaching tool for many years, and undoubtedly stimulated many medical students to explore careers in physiology.

In conclusion, it can be safely stated

that although de Cyon perhaps just missed being one of the great physiologists of his time, his industry and skill should have given him a very high rank. Had his political views been somewhat different, his memory might have been accorded more honor both abroad and in his native land.

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ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Biochemistry

Bezkorovainy A, Grohlich D: Cleavage of transferrin by cyanogen bromide. *Biochim Biophys Acta 263:645, 1972*

Human serum transferrin treated with CNBr and then succinylated was separable into two fractions in w/w ratio of 3-4:1 by gel filtration. The larger fraction, M_r 60 000 was homogeneous and contained all the carbohydrate originally present in transferrin. It separated into at least three fragments upon reduction-alkylation and starch gel electrophoresis. The smaller fraction consisted of two components with an average M_r of 12 000, which were separable by starch gel electrophoresis. When transferrin was reduced-alkylated in addition to the CNBr cleavage and succinylation, it was separable into at least five fragments by starch gel electrophoresis. The iron-binding sites were apparently not localized in a small portion of the protein molecule. It was concluded that transferrin is not a protein consisting of two identical or nearly identical halves.

Bezkorovainy A, Grohlich D: A low-molecular weight protein of bovine colostrum similar to immunoglobulin G. *Amer J Vet Res 32:2081, 1971*

A protein was isolated from bovine colostrum, which had a molecular weight of only 15,000 and contained 6% carbohydrate consisting of sialic acid, N-acetyl glucosamine, and hexose. In the Ouchterlony double diffusion system, it showed a partial identity pattern with bovine serum IgG using the IgG antiserum. Amino acid analysis indicated that the protein was not a random breakdown product of IgG.

Bezkorovainy A, Springer GF, Desai PR: Physicochemical properties of the eel anti-human blood group H(O) antibody. *Biochemistry 10:3761, 1971*

The eel anti-human-group H(O) antibody isolated as described in [this] paper was homogeneous by ultracentrifugal and electrophoretic criteria. It is an FS globulin, has a molecular weight of 123,000, and is of nearly spherical shape. It consists of three physically bonded subunits of apparently identical molecular weight of 40,000. Each subunit consists of four polypeptide chains of identical size; the chains, whose molecular weight is near 10,000, are joined by disulfide linkages.

Chiao MT, Bezkorovainy A: Inhibition of the hemoglobin-haptoglobin interaction by various polyelectrolytes. *Physiol Chem Phys 3:394, 1971*

The mechanism of hemoglobin-haptoglobin interaction was investigated using various polyelectrolytes as inhibitors of the interaction. It was found that best inhibition was provided by those compounds that carried the largest net negative charge. Thus heparin and DNA were the most effective inhibitors; orosomucoid, serum albumin, and the M-2 glycoprotein were moderate inhibitors; and beta-lactoglobulin and immunoglobulins did not inhibit the interaction at all at neutral pH. It was concluded that charge interactions are probably of considerable importance in the hemoglobin-haptoglobin interaction.

Zschocke RH, Chiao MT, Bezkorovainy A: The function of amino groups in the binding of iron by transferrin. *Europ J Biochem 27:145, 1972*

Succinylation and a combination of succinylation with reductive alkylation and trinitrophenylation procedures were used to investigate the function of amino groups of transferrin. It was shown that apo-transferrin had two types of amino groups: those that were easily accessible to chemical modification reagents (60-61 in number) and those that were more difficult to modify (6-7 in number), which were also concerned with the maintenance of the conformation of the protein. The latter type of amino groups became even less accessible to the environment upon the binding of the iron by transferrin. However, the unreactive amino groups were not directly involved in the binding of iron by transferrin, since iron-binding properties could be partially recovered in the extensively succinylated protein. It was concluded that the function of the amino groups in question was probably to stabilize the three-dimensional structure of transferrin.

Gastroenterology

Hardison WGM, Apter JT: Micellar theory of biliary cholesterol excretion. *Amer J Physiol 222:61, 1972*

The relation between biliary bile salt excretion and biliary cholesterol and phospholipid excretion was studied in bile-fistula rats infused with graded doses of bile salt. With infusion of taurocholate, a micelle-forming bile salt, increase in biliary bile salt excretion was associated with an increase in biliary lipid excretion. With infusion of dehydrocholate, a nonmicelle-forming bile salt, biliary lipid excretion increased little. With taurocholate infusion, the relation between biliary bile salt and lipid excretion was not linear. At high bile salt excretion rates, biliary lipid excretion rate increased little in spite of increasing biliary bile salt excretion rate. At very low bile salt and phospholipid excretion rates, cholesterol excretion remained disproportionately high. At low infusion rates, therefore, bile was more nearly saturated or supersaturated with cholesterol than at high rates. Micelle formation appears an important mechanism in biliary lipid excretion, but it alone cannot explain the quantitative relation between biliary bile salt and lipid excretion.

Infectious Disease

Kallick C: Systemic lupus erythematosus associated with haemobartonella-like organisms. *Nature-New Bio 236:145, 1972*

Haemobartonella organisms have been known to cause many animal diseases and are known to infect every animal species. An association between these agents and systemic lupus erythematosus (SLE) was observed. Blood films from eight patients with known SLE were compared with sixteen normal controls by graduate veterinary physicians looking for specific haemotrophic infections resembling animal infections of the haemobartonella group. Examination was by acridine orange and florescein conjugated specific-direct antibody obtained from animals with several kinds of haemotrophic infections. With acridine orange, all eight patients had suggestive erythrocyte structures which resembled haemobartonella agents. Two controls had similar structures. Using direct fluorescein conjugated antibodies, four of eight lupus patients had suggestive structures on the erythrocytes which was stained with conjugated antibody anaplasma marginale and eperythrozoon suis. No controls had similar fluorescence. These findings suggest that an association may exist between haemobartonella-like agents and systemic lupus erythematosus, and indicate further study.

Apter JT: The analog computer as a teaching aid in medical practice and research. *Comp Biol Med 1:113-149, 1971*

A large, general purpose analog computer has been used in conjunction with compartment and other mathematical models to help physicians involved in clinical practice and research to clarify their understanding of the clinical problem. Four problems are described in detail: free-fatty acid conversion to triglycerides in fasting human subjects, facilitation of ovulation in rats, monitoring of base-excess in dogs, regulation of digitalis dosage in humans. Computer-generated solutions of the model equations called attention to details of real data that had been overlooked or attributed to artefact or experimental error.

Apter JT: Analysis of biodynamic loading of the circulatory system. *AMRL Tech Rpt, Wright-Patterson AFB, Ohio TR71-29, 573-594, 1971*

The model developed here was based on the dynamic viscoelastic properties of the components of the cardiovascular system. The model parameters are functions of time and are valid for a wide range of strains. From some limited kinds of behavior numerical values for model parameters can be obtained from data on intact portions of a human cardiovascular system. Almost all behavior can be clarified with this model which, therefore, serves as a valuable teaching aid and as a basis for evaluating the qualitative results to be expected from management of changes induced by large dynamic loads, like impact.

Apter JT: Biosystems modeling, "Models as adjunct to analysis of biological systems," "Viscoelasticity of biomaterials," "Compartmented systems analysis." ***In:*** **Biomedical Engineering Systems,** *Edited by Clynes, M. and Milsum, JH, New York, McGraw Hill, 1970, pp. 165-211*

This chapter . . . consider[s] the what, why, when, and how of models in biological research. What is a model? Why is a model advisable? When is a model necessary? How are models developed and used to make research efficient? Physicists have the answers to these questions.

According to Cyril Stanley Smith, they have developed and used models since at least the seventeenth century to advance their science. Since the most challenging physical problems are those met in living systems, it is fitting to use models to advance research in these systems also. Examples of models which accomplish this end in both the physical and biological sciences will help demonstrate and justify their effective use.

Apter JT: Dynamic compliance of living lungs before and after perfusion. *J Biomech 3:77, 1970*

In situ lungs of living, anesthetized dogs were exposed to adequate ventilatory conditions between short exposures to test conditions for measuring some dynamic properties of the lungs. These properties include the dynamic compliance as a function of respiratory cycle frequency and of stroke (or tidal) volume with the lung tissue in various stages of pre- and post-perfusion conditions. Between test exposures, ventilation was maintained with a respiratory rate of 0-4 Hz and stoke volume of 300 ml. Test exposures for computing dynamic compliance as a function of frequency were a tidal volume of 100 ml and rates from 0-04 Hz to 0-9 Hz. At a tidal volume of 100 ml. the lungs behaved linearly, giving a sinusoidal pressure output to a sinusoidal volume input. Test exposures for finding the pressure-volume relationship were performed at a cycle frequency of 0-4 Hz with stroke volumes from 50 ml to 500 ml. Histologically verified pulmonary tissue changes followed steady (non-pulsatile) pulmonary artery perfusion with whole blood for two hours. The viscoelastic

properties were a function of the condition of the living tissue.

Because the dynamic compliance was a function only of frequency or of volume or of condition of the lung, there was no hysteresis in these records. They were reversible, reproducible, responsive to verified changes in pulmonary tissue and were consistent with contemporary methods for testing other viscoelastic systems. The tests themselves did not endanger pulmonary tissue properties nor interfere with the gaseous exchange function of the lungs. Therefore, the tests could be adapted for clinical measurements of pulmonary mechanics.

Apter JT: Influence of composition on thermal properties of tissues. ***In*** **Biomechanics, its Foundations and Objectives.** *Edited by Fung, YC, New Jersey, Prentice-Hall, 1972, pp. 217-236*

Biological soft tissues (exclusive of bone and cartilage) depend for their mechanical properties on their fibrillar components: Muscle, elastin, collagen and reticulin. The detailed macromolecular (polymeric) structure of these fibrils has been clarified by recent investigations (Huxley, 1957; Hanson and Lowry, 1961; Hoeve and Flory, 1958; Ramachandran, 1967) but is still far from settled. The present discussion [is] limited to consideration of the possible influence of arrangements of the macromolecules on fibrillar behavior and of arrangements of fibrils on tissue behavior, with an emphasis on distinctive thermal responses. The problem is challenging since the macromolecules are found in a variety of arrangements, and rewarding because thermal responses differ markedly from one fibril type to another. A muscle fibril contains thick "filaments" of the proteins myosin and tropomyosin or paramyosin, and thin filaments of actin (Huxley, 1957) . . . These filaments are highly ordered (crystalline) in fibrils of striated and cardiac muscle; less ordered in smooth muscle cells. Collagen also occurs as fibrils with a highly ordered protein structure (Mason, 1965) and therefore is also a crystalline polymer (Ramachandran, 1967). Elastin is an amorphous polymer which does not crystallize even when highly strained (in contrast to rubber); this amorphous state being responsible for special thermal properties of elastin (Hoeve and Flory, 1958).

Apter JT, Berman S: Medical students time-sharing an analog computer to learn physiology. *IEEE Trans Biomed Eng 19:82, 1972*

Medical schools, both newly developing and well-established, are recognizing a need for visual and mechanical instructional aids for teaching medicine to future physicians and paramedical personnel. The analog computer has proved to be very useful for these purposes in our hands, since it can be used to simulate many human and animal functions.

Apter JT, Graessley W: Mathematical development and solution of a physical model for muscular contractile elements. *Proc 5th Ann NASA-University Conf on Manual Control 215:523-540, 1969. Also in AMRL-Tech Rpt 70-60, Wright-Patterson AFB, Ohio, 1-25, 1970*

A self-consistent model based on valid physical and chemical laws known to govern the viscoelastic behavior of polymeric materials was developed to be also consistent with muscular behavior. Exposure of the model to various perturbations like stretch, loading chemical reactions or diffusion of ions replicated events known to take place during stretch, loading and stimulation of muscle, whether smooth or striated. The equations of motion of the model so perturbed were solved with an analog computer which generated stress, strain and strain rate curves for the model. These curves closely resembled real shortening velocity-time curves, isometric tension development and other muscular responses. Therefore it was possible to obtain initial estimates of model parameters from real muscular behavior previously not appreciated, like phase gain-angle and elastic modulus enhancement at critical sinusoidal strain frequencies. The general nature of the model makes it possible to formalize more complex perturbations and to quantify a wide range of muscular behavior in a more useful and reproducible way than before.

Apter JT, Graessley WW: A physical model for muscular behavior. *Biophys J 10:539-555, 1970*

A model for muscular behavior has been developed by a generalization of the laws governing the viscoelastic behavior of polymeric materials. The model simulates events thought to take place during stretch, loading, and stimulation of muscle, whether smooth or striated. The equations of motion were solved with an analog computer for several types of perturbation, and stress, strain, and strain-rate curves were generated. Model parameters were selected by fitting experimental stress-relaxation data. The resulting equations predicted the frequency dependence of dynamic modulus and phase angle within experimental error. With appropriate boundary conditions and suitable values for model parameters, the computed results also closely resembled experimental curves of contraction velocity vs. time, isometric tension development vs. time, force-velocity curves, and temperature-tension relationships. These results call attention to the relationship between the behavior of various kinds of muscle and open the way for quantifying muscular behavior in general.

Apter JT, Graessley WW: Progress in quantification of muscular action. *Proc 6th Ann Conf Manual Control, 165-176, 1970*

In March, 1969, at this conference, we presented a model for muscular behavior that promised to be useful in quantifying muscular action for the purpose of analyzing the capabilities of handicapped individuals and in developing prostheses (Apter and Graessley, 1970). This paper gives a progress report of further work on the model which qualitatively fits a wide variety of muscular behavior, but which had not been tested quantitatively.

Apter JT, Graessley W: A relation between positive phase shift and elastic modulus enhancement of smooth muscle. *Experientia 25:145-147, 1969*

Muscle is a special kind of visco-elastic material capable of synthesizing energy during the contractile process. The mechanical behavior of relaxed smooth muscle can be matched by a three-parameter model composed of a Maxwell element in parallel with a spring. All 3 parameters, essentially 2 tensile moduli to quantify energy-conserving characteristics and 1 viscosity to quantify energy-dissipation, have been measured. These 3 parameters are known to increase with the level of contractile tone so that they may also be a measure of the energy-synthesizing characteristics.

If a sinusoidal strain is imposed on *in vitro* smooth muscle, and on some insect flight muscles, the induced stress is generally out of phase with the strain and at high frequencies the phase angle (angular difference between stress and strain waves) is negative as would be expected for an ordinary viscoelastic body. However, at low frequencies there is a positive phase angle which appears to represent a net production of mechanical energy by the muscle. The present study shows that the same low frequency oscillatory strains also induce a net increase in the contractile tone of smooth muscles, resulting in levels of tensile moduli which equal and even exceed those produced by drugs or electrical stimulation. The purpose of this report is to describe this new phenomenon and to give the conditions for producing it.

Apter JT, Hardison WGM: Estimation of parameters in phospholipid regulation of bile salt stimulated biliary cholesterol excretion. *Proc Ann Nat Elect Conf 26:2-6, 1970*

A clinician or medical research worker often finds it necessary to have numerical values for biological variables not accessible to direct measurement. The necessity arises when the clinician must assess an important human function or when the investigator aims to summarize large groups of data into a few numbers with biological significance. When the numbers define characteristics of the system, they are referred to as *parameters* which must be estimated from numerical values for *variables* measured directly. This presentation will

describe the methods used to obtain numerical values for phospholipid stores [P(0)] and their rate of repletion [E_o] in the liver, for the number x of cholesterol molecules combined with a phospholipid-bile salt complex, for a hepatic bile salt synthesis rate, G, and for an independent cholesterol excretion rate F_o. These parameters were estimated by a variety of methods from measurements of phospholipids P, cholesterol F, and bile salts B in the bile of rats receiving intravenous infusions of known amounts of extraneous bile salts.

The values obtained are of both basic and clinical importance since a satisfactory sequence of intrahepatic events linking bile salt and lipid excretion has never been set forth and tested quantitatively and could be analyzed with these measurements if properly used. The problem was approached in several ways. The first step was to develop a model based on valid physical and chemical laws, but consistent with events known to take place or reasonably assumed in the real system in question. The laws were expressed as differential equations which yielded readily to solution with an analog computer. The forcing function of the equations was matched to the experiments performed on rats so that the computer-generated solutions would match real data qualitatively and quantitatively if the model and parameter values were reasonable; and they did. Experimental data provided initial estimates of the model parameters for each animal; then the parameter values were varied by a rough scanning procedure until the computer matched data reasonably. The final values of the parameters served to summarize all the data on a single animal so that animals could be tested for responses to external influences and could be compared with each other.

The model was sufficient to supply all the wanted parameters: x, F_o, G, P(0), and E_o so long as ample hybrid computer power was available so that a sensitive and unique method for estimating parameters in a non-linear system could be used. However, if such power is not available, the data can still give the parameter values if suitably handled. This presentation describes the techniques used with the analog computer power at our disposal.

The physical and chemical laws governing the model were expressed as a series of kinetic equations to be consistent with the following reasonable, but hypothetical, sequence of intrahepatic events linking biliary bile salt and lipid excretion rates. The hypothesis includes the following assumptions: (1) cholesterol (F) and phospholipid (P) excretion is a result of micelle formation with bile salts (B) in the liver; (2) availability of P largely determines the capacity of the micelle for F; (3) hepatic P destined for biliary excretion exists in a separate pool which can be depleted; (4) repletion of this pool either by synthesis or by transfer from another pool is rate-limited. Assumptions 1-3 are based on current knowledge; 4 is unproven but reasonable; no restriction is placed on F. The kinetic equations were solved with an analog computer.

Apter JT, Marquez E, Janas M: Dynamic viscoelastic anisotropy of canine aorta correlated with aortic wall composition. *J Ass Adv Med Instrum 4:15, 1970*

Longitudinal strips from 14 locations along the aortas of dogs were stretched sinusoidally at frequencies from 0.01 to 10 Hz. *In vivo* longitudinal strain levels were ascertained before these tests and were matched and exceeded during them. The behavior of these strips was compared with the behavior in the circumferential direction and with the behavior of isolated aortic elastin and collagen and of stimulated aortic wall smooth muscle. At strains less than those found *in vivo*, the aorta was generally isotropic, like elastin. At higher strains, matching those found *in vivo*, the upper thoracic aorta behaved like elastin and, again, was isotropic. In contrast, the lower thoracic and abdominal aortas strained to *in vivo* levels behaved like collagen longitudinally and like elastin circumferentially. At still higher strains, where the strain and stress levels were associated with collagen-like properties, anisotropy was characterized by a higher modulus in the longitudinal than in the circumferential direction. If a slightly strained aorta was stimulated with phenylephrine hydrochloride, the aorta was isotropic and revealed the presence of smooth muscle.

Apter JT, Mason P: Dynamic mechanical properties of mammalian ureteral muscle. *Amer J Physiol 221:226, 1971*

This study gives a description and measurements of the mechanical properties of ureters

isolated from anesthetized dogs and calves, in particular the stress response to step-function and sinusoidally oscillating strains. A step-function extension strain of a strip of the ureter was accompanied by a sharp rise in stress which fell along an essentially exponential course (stress relaxation) to be followed by a single or by repeated recontractions, depending on temperature, ionic environment, and strain level. A sinusoidally oscillating strain was accompanied by an oscillating stress which sometimes led (as for inert viscoelastic material) and sometimes lagged (as for muscle) behind the strain, depending on the oscillation frequency. In addition, the stress, though oscillating, was nonlinear since it was not sinusoidal except for very small strains and at frequencies higher than .8 Hz. Quantification of these data as system parameters was accomplished by referring to a simplified idealized physical system which responds to similar strains with similar stress behavior; that is, with recontraction, phase leads, phage lags, and nonlinearities, thus strongly resembling ureteral specimens.

Apter JT, Mason P, Lang G: Urinary bladder wall dynamics. *Invest Urol 9:520, 1972*

Methods used to study the flow of fluids through chambers with viscoelastic walls are applied here to analysis of urinary bladder pressures. In addition, methods used to study the viscoelastic properties of polymers are applied rigorously to analysis of bladder wall behavior. These theoretical and experimental analyses show how it would be possible to quantify pressure data obtained in cystometry during health and disease.

The pressure data obtained from experiments or clinical tests performed in some convenient way (e.g., step-wise injections of fluid) were used to compute the bladder wall properties as they exist *in vivo*. Stress-strain data obtained from *in vitro* studies of bladder wall properties were correlated with the histological structure of the muscle, elastin and collagen in the bladder wall. These correlations provide a firm basis for urologists to use in diagnosing disease pathology from *in vivo* studies of cystometry.

Morehouse F, Apter JT, Amiot L: Use of hybrid computer to analyze behavior of detailed model for aortic blood flow. *Comput Biol Med 1:29, 1970*

A model, based on the physical principles of energy and material balance, was developed to be consistent with the anatomy and physiology of certain aspects of the cardiovascular system. Mathematical expression of these laws was not amenable to analytic solution but yielded to a hybrid computer solution which generated aortic pressure curves closely resembling real ones. By optimizing the match between model and real aortic pressure curves the computer system facilitated estimation of model parameters for cardiac ejection curves (or blood flow curves) as they might appear at various locations down the aorta. The parameter variations were consistent with reality since they required loss of blood via tributaries down the aorta and attenuation and dispersion due to damping by aortic wall properties. A model this reliable would be necessary if aortic pressure curves were to be analyzed to provide estimates of human stroke volume or cardiac output.

Wilson D, Apter JT, Schwartz F: A model for measuring renal blood flow from the plasma disappearance of iodopyracet. *J Appl Physiol 28:79, 1970*

A nonlinear multicompartmented model was developed to be in accord with current understanding of the behavior of iodopyracet (Diodrast) in dogs. Material balance relations applied to each compartment led to equations for the model which was tested in six anesthetized dogs with one kidney removed. The time course of Diodrast plasma concentration changes measured, after a single dose and during infusion, in renal artery and vein as well as in red cells, liver, and muscle established the validity of the model with the assistance of an analog computer solution of the equations. Suitable analysis of these data, using initial slopes and extrema, permitted use of mixed venous blood concentrations, alone, to compute renal plasma flow and renal extraction ratio in four other dogs as well. A large digital computer programmed to use a nonlinear parameter estimation technique utilized these

computations as initial estimates, and all the data as well, to find more accurate values for renal plasma flow and extraction ratio and then to generate computed data for comparison with actual data. Plasma flow and extraction ratio computed this way did differ very little ($P<0:05$) from clearances measured during constant infusion of para-aminohippurate. This success suggests that the model may serve as the basis for clinical measurements of these parameters.

Neurology

Garron DC, Klawans HL Jr, Narin F: Intellectual functioning of persons with idiopathic parkinsonism. *J Nerv Ment Dis 154:445, 1972*

Initial data from an investigation of intellectual functioning of patients with parkinsonism is reported. Forty-seven white, American-born, noninstitutionalized persons with idiopathic parkinsonism and without any other demonstrable disease of the central nervous system, and a matched group of controls were studied. Subjects were given four tests of intellectual ability adapted from Guilford's comprehensive model of intelligence. A method of testing with a computer was employed so that patients could test themselves repeatedly with alternate and equivalent forms.

Analysis of the time scores led to the division of patients into two groups, a faster group with a time distribution similar to their controls, and a slower group of patients who were slower than their controls on all four tests. The slower group is significantly older and significantly more disabled, but has not had parkinsonism significantly longer than the faster group. The slower patients generally score somewhat lower in intellectual ability than their controls, while intellectual ability of the faster patients seems unimpaired when compared to their controls. These results suggest that akinesia may be more characteristic of patients in whom the onset of the disease is late in life, and that late onset and akinesia tend to be associated with intellectual deterioration.

Urology

Flanagan MI: Transperineal urethral resection of the prostate. *J Urol 107: 1028, 1972*

Postoperative stricture of the anterior urethra after endoscopic resection of the prostate is a significant, potentially disabling and common occurrence. To reduce or eliminate the occurrence of post-transurethral resection stricture, in 1966 I initiated routine perineal urethrostomy when an endoscopic operation on the prostate was performed. This method, described as transperineal urethral resection of the prostate, has been done on more than 300 patients and is the basis of this report.

Transperineal urethral resection is an acceptable and highly desirable alternative to transurethral resection when an endoscopic operation is performed on the prostate.